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CONTENTS

M E D I C I N S K I P R E G L E D
ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA
Novi Sad *Vase Stajića 9* *Srbija*

Med Pregl 2026; LXXIX (3-6): 59-156. Novi Sad: mart-juni.

SADRŽAJ

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EDITORIAL
UVODNIK

DO WE REALLY KNOW RENAL FUNCTION BEFORE ZOLEDRONATE INJECTION

DA LI ZAISTA ZNAMO FUNKCIJU BUBREGA PRE INJEKCIJE ZOLEDRONATA

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Editorial
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I recently attended a presentation by a bone specialist on the proposed use of intravenous zoledronate after hip fracture. I fully understand and strongly support the clinical objective of improving access to effective secondary fracture prevention in this highly vulnerable population. Intravenous zoledronate is an effective and pragmatic treatment option, and the under-treatment of patients after hip fracture remains a major clinical problem. However, I was struck by the central role given to Cockcroft–Gault creatinine clearance in the proposed renal decision pathway.

Cockcroft–Gault equation is outdated, and its historical use in drug labelling should not be conflated with physiological superiority or individual accuracy. The equation estimates creatinine clearance rather than true glomerular filtration rate (GFR); it was developed before modern IDMS-traceable creatinine assays and performs poorly against measured GFR. This has been demonstrated in a large analysis of creatinine-based equations specifically adapted to the context of drug dosage adjustment. GFR was expressed in non-indexed mL/min and validated against measured GFR in 14,804 participants. Of all equations tested - including MDRD, CKD-EPI, LMR and EKFC - Cockcroft–Gault performed worst across key metrics: bias, imprecision, P30 accuracy and correct classification into GFR categories. The authors concluded that Cockcroft–Gault should not be used for drug dosage decisions [1,2].

A further difficulty is that Cockcroft–Gault is sometimes perceived in geriatric practice as a "safer" or more conservative equation for older patients because it often gives lower values than CKD-EPI in frail or low-weight individuals. This perception is misleading. Cockcroft–Gault is mathematically driven by the term *(140 – age)* multiplied by body weight, making both age and weight major determinants of the result. In frail older patients, low body weight may markedly reduce the calculated creatinine clearance; conversely, in obese patients, use of actual body weight may produce the opposite effect. The direction and magnitude of the discrepancy are therefore not consistent. More importantly, a lower result does not imply greater proximity to measured GFR. In studies comparing creatinine-based equations with measured GFR in a drug-dosing context, Cockcroft–Gault performed worse than modern equations across key metrics, including EKFC, in terms of bias, precision, accuracy and GFR category classification [1,2].

I was also struck when a member of the audience proposed CKD-EPI equation [3] as a straightforward alternative. This is not a fully satisfactory solution, particularly in older adults. CKD-EPI is known to overestimate GFR in older individuals, whereas the EKFC equation [4], - specifically developed and validated in Europe - was designed to improve age modelling and reduce age-related bias across the full age spectrum. EKFC is now recommended by the European Federation of Clinical Chemistry and Laboratory Medicine for use in European laboratories [5,6]. However, EKFC should not be applied uncritically for drug dosing decisions [7]. For drug dosage adjustment, the clinically relevant quantity is not GFR normalised to 1.73 m^2, but the patient's absolute excretory kidney function, expressed in mL/min. Drug clearance depends on the individual patient's absolute filtration capacity, not on the value that would be obtained if their body surface area were 1.73 m^2. Accordingly, when CKD-EPI, EKFC or any indexed eGFR equation is used for drug-dosing purposes, the result should be de-indexed according to body surface area. This point is especially important in frail older

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patients following hip fracture, who frequently have low body weight and low body surface area [2].

Even this, however, does not fully resolve the problem. All creatinine-based equations remain estimates. Their standard performance metric – the P30 – defines an estimate as accurate if it falls within ±30% of measured GFR. Around a decision threshold of 30 mL/min, this level of uncertainty is clinically substantial: a measured GFR of 30 mL/min may correspond to an estimated value between 21 and 39 mL/min and still be considered "accurate". For Cockcroft–Gault, the problem is even more pronounced still: among patients with a measured GFR of 30–45 mL/min, the P30 is only 63.5%; among those with a measured GFR of 15–30 mL/min, it falls to 49.5% [2]. In other words, precisely within the range where renal thresholds for zoledronate become clinically relevant, Cockcroft–Gault provides a highly uncertain estimate.

This is not merely a statistical concern. Frail older patients following hip fracture are precisely those in whom creatinine-based estimation is most unreliable: sarcopenia, acute illness, perioperative changes, hydration status, diuretic use and non-steady-state creatinine can all undermine the validity of any equation. A patient calculated at 32 mL/min by Cockcroft–Gault, CKD-EPI or even de-indexed EKFC may have a true measured GFR that is substantially lower or higher. A value in the region of 30–35 mL/min should therefore be interpreted as a zone of uncertainty, not as a reliable individual measure of renal function [8].

This concern is particularly relevant when the drug in question is potentially nephrotoxic, or when the clinical decision hinges on a narrow renal threshold. The importance of measured GFR has already been emphasised in the context of drugs such as cisplatin, but the principle is broader: when the consequences of misclassification are clinically significant, reliance on creatinine-based estimation may be insufficient [2].

In this setting, arbitrating between Cockcroft–Gault, CKD-EPI and EKFC when a patient is close to the renal threshold is not a productive approach. Cockcroft–Gault is outdated and poorly performing; CKD-EPI is problematic in both younger and older adults; EKFC is a more appropriate modern European estimate, but for drug dosing, it must be de-indexed and, even then, remains an estimate rather than a measurement. If renal function is truly central to the decision to administer intravenous zoledronate, the scientifically robust approach is to measure GFR directly.

In my view, plasma iohexol clearance is the most appropriate solution. It provides a true measured GFR, is feasible in routine clinical laboratory practice, and avoids the false precision of creatinine-based equations. This is not an exotic or poorly standardised approach. The European Kidney Function Consortium has recently published a consensus paper in *Kidney International* dedicated to the standardisation of plasma iohexol clearance measurement in adults, covering patient preparation, iohexol administration and safety, blood sampling strategies, laboratory analysis, GFR calculation and implementation procedures [9]. Furthermore, iohexol measurement can be embedded in a laboratory quality assurance framework: laboratories performing iohexol assays may participate in external quality assessment schemes, which is essential for reproducibility and inter-laboratory comparability [10].

This approach is consistent with European laboratory recommendations. The EFLM recommendations based on KDIGO 2024 address iohexol plasma clearance standardisation and support broader implementation of appropriate GFR assessment strategies across European laboratories [5]. In this context, measured GFR by plasma iohexol clearance should not be regarded as a luxury, but as the appropriate test when a binary treatment decision depends on a narrow renal threshold in a frail older patient.

The central question is therefore not whether the cut-off should be 30 or 35 mL/min, nor whether Cockcroft–Gault should be replaced by CKD-EPI. The real issue is whether it is acceptable to base a binary safety decision in frail older patients on an imprecise creatinine-based estimate. When the degree of uncertainty is large, and the consequences of misclassification are clinically relevant, measured GFR by standardised plasma iohexol clearance, performed within a quality-controlled laboratory framework, is not a luxury; it is the appropriate test.

References

1. Delanaye P, Björk J, Courbebaisse M, Couzi L, Ebert N, Eriksen BO, et al. Performance of creatinine-based equations to estimate glomerular filtration rate with a methodology adapted to the context of drug dosage adjustment. Br J Clin Pharmacol. 2022;88(5):2118-27.

2. Delanaye P, Guerber F, Scheen A, Ellam T, Bouquegneau A, Guergour D, et al. Discrepancies between the Cockcroft-Gault and Chronic Kidney Disease Epidemiology (CKD-EPI) equations: implications for refining drug dosage adjustment strategies. Clin Pharmacokinet. 2017;56(2):193-205.

3. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

4. Pottel H, Björk J, Courbebaisse M, Couzi L, Ebert N, Eriksen BO, et al. Development and validation of a modified full age

spectrum creatinine-based equation to estimate glomerular filtration rate. Ann Intern Med. 2021;174(2):183-91.

5. Cavalier E, Zima T, Datta P, Makris K, Schaeffner E, Langlois M, et al. Recommendations for European laboratories based on the KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Clin Chem Lab Med. 2024;63(3):525-34.

6. Delanaye P, Schaeffner E, Cozzolino M, Langlois M, Plebani M, Ozben T, et al. The new, race-free, Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equation to estimate glomerular filtration rate: is it applicable in Europe? A position statement by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). Clin Chem Lab Med. 2022;61(1):44-7.

7. Delanaye P, Cavalier E, Pottel H, Mariat C. Where is the eye of the storm of eGFR formulas? Nephrol Dial Transplant. 2026;41(5):805-7.

Rad je primljen 23. IV 2026.
Prihvaćen za štampu 23. IV 2026.
BIBLID.0025-8105:(2026):LXXIX:3-6:63-65.

8. Johansen A, Sahota O, Dockery F, Black AJ, MacLullich AMJ, Javaid MK, et al. Call to action: a five nations consensus on the use of intravenous zoledronate after hip fracture. Age Ageing. 2023;52(9):afad172.

9. Ebert N, Schaeffner E, Seegmiller JC, van Londen M, Bökenkamp A, Cavalier E, et al. Iohexol plasma clearance measurement protocol standardization for adults - a consensus paper of the European Kidney Function Consortium. Kidney Int. 2024;106(4):583-96.

10. Isakov I, Čabarkapa V, Srđenović-Čonić B, Kladar N, Ilinčić B, Burić D. Status of tryptophan metabolites in different stages of chronic kidney disease of non-diabetic etiology. Med Pregl. 2022;75(1-2):5-11.

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ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

DEEP LEARNING-BASED CLASSIFICATION OF COLORECTAL ADENOMAS – A DATA-DRIVEN MODEL FOR RESOURCE EFFICIENCY

KLASIFIKACIJA KOLOREKTALNIH ADENOMA ZASNOVANA NA DUBOKOM UČENJU – MODEL ZASNOVAN NA PODACIMA ZA EFIKASNOST RESURSA

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Abstract
We evaluated the performance and practical impact of several deep learning models, including ResNet and transformer-based architectures, for classifying colorectal adenomas with and without high-grade dysplasia in histopathology images, to support an artificial intelligence-assisted triage workflow that reduces pathologist workload while maintaining diagnostic quality and workflow efficiency. Models were trained and validated on 1,669 histopathology image tiles from colorectal polyp samples (368 with high-grade dysplasia, 767 low-grade adenomas, and 534 non-neoplastic controls) that were expert-reviewed and analysed at 100× magnification. Performance was assessed using 5-fold cross-validation, and Grad-CAM++ heat maps were generated to visualise model attention and support explainable pathologist review. ResNet101 achieved 99.17% accuracy in the best fold and 97.40% on average. The explanatory heat maps consistently highlighted diagnostically relevant epithelial regions, supporting rapid pathologist verification. In a simulated workflow of 1,000 colorectal polyps, artificial intelligence-assisted triage reduced pathologist review volume by 41–61% while maintaining 98.91% detection accuracy for high-grade dysplasia and 99.47% accuracy for adenomas without high-grade dysplasia. These reductions correspond to meaningful full-time equivalent savings in high-volume gastrointestinal pathology practice, where repetitive biopsy assessment contributes substantially to the daily workload. These findings indicate that deep learning models can accurately classify colorectal adenomas and detect high-grade dysplasia, and that artificial intelligence-assisted triage and sign-out, supported by interpretable heat maps, may provide a practical pathway towards more sustainable and efficient digital pathology workflows.
Key words: Colorectal Neoplasms; Adenoma; Polyps; Deep Learning; Artificial Intelligence; Machine Learning; Computer-Assisted Diagnosis; Pathology

Sažetak
Procenili smo performanse i praktičan uticaj nekoliko modela dubokog učenja, uključujući *ResNet* i arhitekture zasnovane na transformerima, za klasifikaciju kolorektalnih adenoma sa displazijom i bez nje, visokog stepena na histopatološkim slikama, sa ciljem podrške radnom toku trijaže uz asistenciju veštačke inteligencije kako bi se smanjilo opterećenje patologa uz održavanje dijagnostičkog kvaliteta i efikasnosti radnog toka. Modeli su obučavani i validirani na 1.669 histopatoloških slika pločica iz uzoraka kolorektalnih polipa (368 sa displazijom visokog stepena, 767 adenoma niskog stepena i 534 ne-neoplastička kontrola) koje su pregledali stručnjaci i analizirali pri uvećanju od 100 puta. Performanse su procenjivane korišćenjem 5-podeljene unakrsne validacije, a Grad-CAM++ toplinske mape su generisane kako bi se vizualizovala pažnja modela i podržao objašnjivi pregled od strane patologa. *ResNet*101 je postigao tačnost od 99,17% u najboljoj grupi i u proseku 97,40%. Objašnjavajuće toplotne mape dosledno su isticale dijagnostički relevantne epitelne regije, podržavajući brzu verifikaciju od strane patologa. U simuliranom toku rada sa 1.000 kolorektalnih polipa, AI-podržana trijaža smanjila je obim pregleda od strane patologa za 41–61%, dok je održala tačnost detekcije od 98,91% za displaziju visokog stepena i 99,47% za ne-HGD adenoma – za benigni (nekancerozni) tumor žlezdanog tkiva. Ova smanjenja odgovaraju značajnim uštedama ekvivalenta punog radnog vremena u praksi gastrointestinalne patologije sa velikim obimom, gde ponovljene procene biopsija značajno doprinose svakodnevnom radnom opterećenju. Ovi nalazi ukazuju na to da modeli dubokog učenja mogu precizno klasifikovati kolorektalne adenome i detektovati displaziju visokog stepena, kao i da AI-podržana trijaža i zatvaranje pregleda, podržani interpretabilnim toplotnim mapama, mogu pružiti praktičan put ka održivijim i efikasnijim tokovima digitalne patologije.
Ključne reči: kolorektalni tumori; adenoma; polipi; duboko učenje; veštačka inteligencija; mašinsko učenje; kompjuterski asistirana dijagnoza; patologija

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Abbreviations

AI – artificial intelligence
CLIA – Clinical Laboratory Improvement Amendments
BMSs – biomedical scientists
GI – gastrointestinal
HGD – high-grade dysplasia
CNNs – convolutional neural networks
FTE – full-time-equivalent
ViT – Vision Transformer
DeiT – Data-efficient Image Transformer

Introduction

The field of histopathology is undergoing a shift as artificial intelligence (AI) is integrated into high-volume, low-complexity diagnostic tasks. The aim is to reduce specialist pathologist workload while improving workflow efficiency and resource allocation. Earlier workload-reduction strategies began with the American Society for Clinical Pathology's certification of cytotechnologists in the United States in 1957.

Later advances introduced digital and computer-assisted cytology screening systems, while maintaining compliance with Clinical Laboratory Improvement Amendments (CLIA '88) requirements that at least 10% of negative gynecologic cytology cases undergo rescreening and that all atypical cases be reviewed by a pathologist [1]. Automation therefore redistributed workload and allowed pathologists to focus on diagnostically complex cases.

In the United Kingdom, biomedical scientists (BMSs) have also adopted expanded roles in histopathology, particularly in gastrointestinal (GI) pathology, to help manage rising diagnostic volumes. This redistribution of routine tasks reduces consultant workload and supports an integrated team approach that improves efficiency while maintaining diagnostic quality [2]. These models demonstrate that structured task-sharing systems can support both service delivery and workforce sustainability.

In the United States, gastrointestinal endoscopy is performed at very high volumes, with an estimated 10–20 million endoscopies and colonoscopies annually [3-5]. Adenomatous polyps account for approximately 60–70% of colorectal lesions considered precursors to invasive carcinoma. Adenoma detection rates are estimated at 31–39% of endoscopies [6], while the risk of high-grade dysplasia (HGD) rises from 2.7–10% in small polyps to 51–85% in large polyps [7,8]. The large number of benign and low-grade adenomas requiring histologic assessment creates a substantial repetitive workload burden within GI pathology services.

Deep learning models, such as convolutional neural networks (CNNs) and transformer-based architectures, have demonstrated high precision in histologic image classification [9]. In pathology, these systems can replicate recognition of epithelial structures, nuclear atypia, and glandular patterns used by pathologists to grade dysplasia. When properly validated and implemented, AI systems may automate repetitive tasks, improve standardisation, and support more resource-efficient diagnostic service delivery [10].

Colorectal adenomas provide an ideal setting for this approach. Differentiating normal mucosa, low-grade adenomas, and HGD is morphologically straightforward but highly repetitive and time-consuming at scale [11]. Hospitals worldwide face increasing demands to deliver more care with fewer personnel and limited budgets. Within diagnostic services, pathology departments must balance rising specimen volumes with static or reduced staffing levels. Efficient management of workflow, turnaround time, and full-time-equivalent (FTE) allocation has therefore become a strategic priority. By assessing both diagnostic performance and operational impact, this study explores how AI-assisted digital pathology may function not only as a technical innovation but also as a practical tool for workflow redesign, workforce planning, and sustainable service delivery.

Material and Methods

Dataset

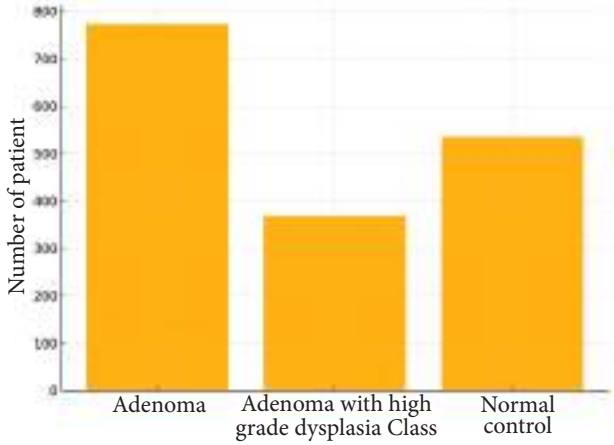
A total of 1,669 histopathological image patches of whole-slide colorectal tissue were analysed. Each patch had a resolution of 2,560 × 1,920 pixels and was captured as a JPG at 100× magnification using a Leica DMC 4500 camera mounted on a Leica DM 2000 LED microscope (Leica Microsystems, Wetzlar, Germany). Images were manually labelled into three diagnostic categories: adenoma (n=767, 46%), adenoma with high-grade dysplasia (n=368, 22%), and normal control tissue (n=534, 32%) **(Table 1; Graph 1).**

Test dataset

For evaluation, a fixed test dataset of 240 images (14.4% of the total) was held out from all cross-vali-

Table 1. Number of images per class in the dataset (N=1,669)

Class	Images	Share (%)
Adenoma	767	46
Adenoma with high-grade dysplasia	368	22
Normal control	534	32



Graph 1. Image count per class in the complete dataset

dation experiments. It contained 80 images per class, ensuring balanced distribution and comparability across models **(Graph 2).**

Model architectures

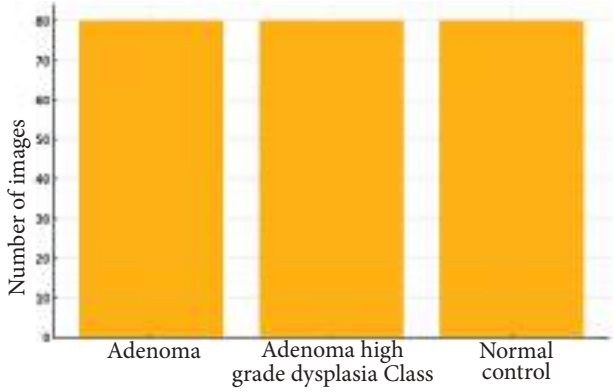
Two families of deep learning models were evaluated. Residual Networks (ResNet-18, ResNet-50, and ResNet-101) were tested as convolutional neural networks with skip connections, using resized inputs of 640 × 480 pixels. Transformer-based architectures included the Vision Transformer (ViT) and the Data-efficient Image Transformer (DeiT), both trained with input resized to 224 × 224 pixels.

Training protocol

All models were trained using 5-fold stratified cross-validation to preserve class balance. ResNet-101 was initialised with ImageNet-pretrained weights; the final fully connected layer was modified to match the three diagnostic categories, and all parameters were fine-tuned end-to-end. Training employed the AdamW optimiser (initial learning rate 1×10^{-4}, weight decay 1×10^{-4}) with a ReduceLROnPlateau scheduler. Each model was trained for 30 epochs per fold.

Hyperparameter optimization

Architecture-specific optimisation was performed with the Optuna framework, varying optimiser, learning rate, weight decay, and scheduler parameters.



Graph 2. Number of images per class in the fixed test dataset

Explainability

To support clinical interpretability, Gradient-weighted Class Activation Mapping++ (Grad-CAM++) was applied to generate class-specific heat maps that highlight the histological regions most relevant to each prediction.

Results

Baseline performance

Baseline performance is summarised in **Table 2.** ResNet architectures achieved the strongest results, with ResNet-101 and ResNet-18 both reaching 96.67% accuracy in the best fold. On average, ResNet-101 achieved 94.75% accuracy compared with 93.92% for ResNet-18, while transformer models performed worse (ViT, 85.10%; DeiT, 92.90%). Importantly, at this stage, ResNet-101 correctly identified the majority of HGD cases, though three HGD cases were misclassified as adenomas and three adenomas were misclassified as HGD. This demonstrates strong, though not perfect, separation of dysplastic from non-dysplastic lesions.

Confusion matrix analysis

The baseline confusion matrix for ResNet-101 **(Figure 1)** shows excellent classification for normal controls, with only 1 error among 80 cases. Adenomas without HGD were also detected with high accuracy, though a small proportion overlapped with

Table 2. Baseline accuracies on the fixed test set (5-fold cross-validation)

Model	Best fold accuracy (%)	Average accuracy (%)
ResNet-18	96.67	93.92
ResNet-50	95.83	94.42
ResNet-101	96.67	94.75
ViT	86.25	85.10
DeiT	95.00	92.90

Table 3. Accuracy after Optuna hyperparameter optimisation

Model	Best fold accuracy (%)	Average accuracy (%)
ResNet-101	99.17	97.40
ViT	97.08	96.30
DeiT	96.67	95.25

HGD. Conversely, HGD was detected in more than 95% of cases, confirming the model's capacity to flag advanced lesions while revealing the main challenge lies in distinguishing borderline adenomas.

Hyperparameter optimisation

Across the complete dataset using 5-fold cross-validation, HGD detection reached 98.91%, adenomas without HGD 99.47%, and normal controls nearly 100%. On the independent hold-out test set, the optimised ResNet-101 model correctly classified 78 of 80 HGD images (97.5%) **(Table 3, Figure 2).**

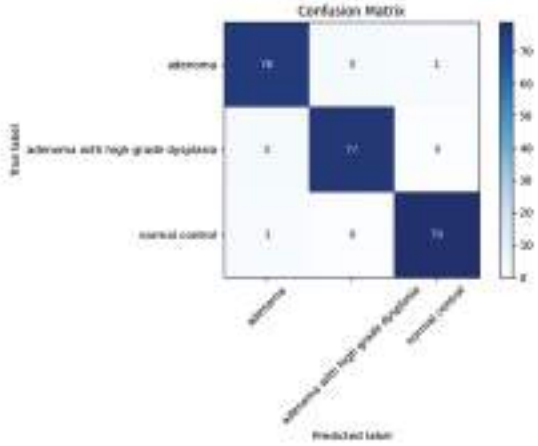


Figure 1. Confusion matrix of the baseline ResNet101 model on the test set

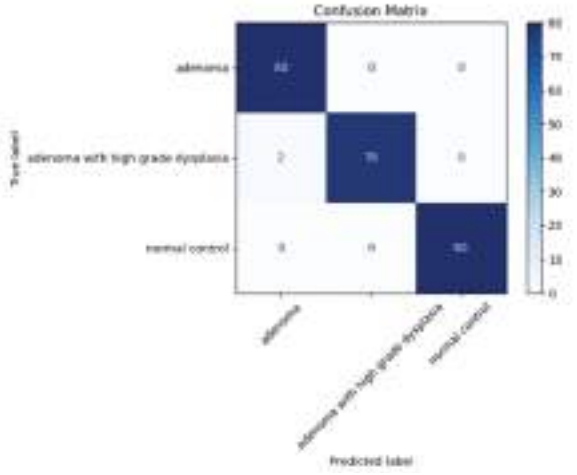


Figure 2. Confusion matrix of the optimised ResNet101 model after Optuna hyperparameter tuning

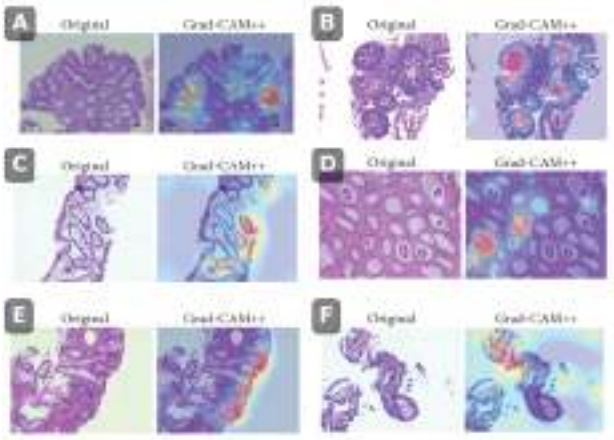


Figure 3. Grad-CAM++ visualisations of model attention for selected test images

Legend: (A) Adenoma without high-grade dysplasia: H&E (left) and heat map (right) showing regions evaluated as adenoma without high-grade dysplasia; (B) Adenoma with high-grade dysplasia: H&E (left) and heat map (right) showing regions evaluated as adenoma with high-grade dysplasia; (C) Normal colonic mucosa: H&E (left) and heat map (right) showing regions evaluated as normal colonic mucosa; (D) Normal colonic mucosa misclassified as adenoma without high-grade dysplasia: H&E (left) and heat map (right); (E) Adenoma without high-grade dysplasia misclassified as adenoma with high-grade dysplasia: H&E (left) and heat map (right): (F) Adenoma without high-grade dysplasia misclassified as normal colonic mucosa: H&E (left) and heat map (right), showing absence of a focused region of evaluation.

Explainable AI results

Grad-CAM++ heat maps **(Figure 3)** showed that ResNet-101 focused on epithelial regions with nuclear atypia and glandular irregularity, the same features pathologists use to diagnose HGD. The alignment of network attention with diagnostically relevant structures supports clinical confidence, indicating that high accuracy in HGD detection corresponds to recognition of the correct microscopic features rather than spurious artefacts.

Discussion

This study demonstrates that deep learning can be integrated into diagnostic histopathology not merely as a technical adjunct, but as a practical framework for workflow redesign and management-level change. By focusing on colorectal adenomas - a high-volume, relatively low-complexity diagnostic category - we demonstrate how validated AI performance can be translated into measurable operational outcomes, including reduced workload, improved effi-

ciency, and potential FTE savings in gastrointestinal pathology services [12]. Similar to how cytotechnologists and biomedical scientists have historically supported specialist pathologists by prescreening routine cases, AI may assume responsibility for common lesions while pathologists to focus on diagnostically complex or clinically significant specimens [13]. This tiered diagnostic model aligns with the broader trend toward task-shifting and workforce optimisation in laboratory medicine [14].

Evidence from multiple disciplines supports the feasibility of this approach. In prostate cancer screening, AI-assisted triage reduced the number of biopsy cores requiring pathologist review by nearly 80% while maintaining detection of clinically significant disease [15]. Likewise, a meta-analysis of radiology workflows demonstrated that AI integration reduced reading volume by 44–62% and reading time by approximately 27% while improving sensitivity without compromising specificity [16]. A large systematic review of more than 152,000 whole-slide images across 100 pathology studies further confirmed that AI systems can achieve expert-level diagnostic performance, with pooled sensitivity of 96.3% and specificity of 93.3% [9]. Together, these findings demonstrate that AI can safely serve as a prescreening and workload redistribution tool across diagnostic specialities. In other areas of medicine, AI systems have also been shown to screen, follow up, and manage patients while reducing consultant workload and supporting service efficiency, including within orthopaedic fracture liaison services [17].

Our study extends this concept to colorectal adenomas. The optimised ResNet-101 model achieved a best-fold accuracy of 99.17% and an average accuracy of 97.40%. Across the entire dataset, using 5-fold cross-validation, the model correctly identified 364 of 368 adenomas with HGD (98.91% detection rate) and 99.47% of adenomas without HGD. In the independent hold-out test set, the optimised model correctly classified 78 of 80 HGD cases (97.5%), while all adenomas without HGD and all normal control cases were correctly classified **(Figure 4).** Errors across the entire dataset were limited, with only three adenomas overcalled as HGD, one adenoma labelled as normal mucosa, and four HGD lesions missed. Importantly, the model achieved near-perfect recognition of normal mucosa and low-grade lesions, a feature with direct operational relevance, as accurate exclusion of low-risk tissue reduces unnecessary manual review and allows pathologists to redistribute time to clinically demanding cases. These findings are consistent with previous work in gastrointestinal pathology, including the study by Faghani et al., which demonstrated high sensitivity and specificity for deep learning detection of dysplasia in Barrett's oesophagus [18].

Beyond diagnostic accuracy, our findings demonstrate how validated AI output can function as an operational management tool. In modelled clinical workflows, AI could independently evaluate diminutive low-risk adenomas, while pathologists selectively review larger lesions, AI-flagged HGD cases, and a proportion of AI-negative cases for quality assurance. Applying published polyp size distributions, this approach would reduce pathologist review volume by approximately 41–61%, corresponding to a potential saving of approximately 0.5 FTEs in high-volume gastrointestinal pathology practice, where daily colonoscopy biopsy volumes are substantial [8]. Such gains do not represent the replacement of professional expertise, but rather redistribution of cognitive effort from repetitive visual confirmation to integrative diagnostic interpretation, multidisciplinary discussion, and consultative activities.

These projected efficiency gains are supported by emerging real-world implementation data. In a community pathology laboratory, practical AI deployment reduced turnaround times by approximately nine hours and decreased immunohistochemistry utilisation by one-third without compromising diagnostic quality [19]. If replicated at scale, such workflow improvements could help alleviate workforce shortages, reduce burnout, and improve service sustainability within increasingly pressured pathology systems.

Explainability remains essential for clinical adoption. AI systems cannot function as "black boxes" if they are to be trusted in routine diagnostic workflows. Historical parallels exist in haematology, where automated blood film analysers identify atypical cells for operator review while achieving performance comparable to experienced laboratory scientists. In histopathology, explainability tools such as Grad-CAM++ heat maps provide a similar interpretive bridge between algorithmic prediction and human review. Retamero et al. demonstrated that AI-assisted detection of breast cancer lymph node metastases improved sensitivity among less-experienced pathologists and reduced review time by directing attention to diagnostically relevant regions [20]. In our study, Grad-CAM++ heat maps consistently focused attention on epithelial regions demonstrating nuclear atypia and glandular irregularity – the same morphologic features used by pathologists to distinguish low-grade from high-grade dysplasia. In misclassified cases, however, heat maps occasionally failed to emphasise dysplastic regions,

instead highlighting benign structures, illustrating both the promise and current limitations of explainable AI systems.

From a systems perspective, these findings support a broader framework for data-driven resource management within pathology departments. Once validated prospectively, AI-generated diagnostic metrics could inform staffing models, identify workflow bottlenecks, guide workload balancing across sites, and support evidence-based allocation of personnel resources [10]. In this way, AI evolves from a purely diagnostic technology into a strategic management tool that supports hospital-level operational decision-making [21].

Several limitations should be acknowledged. The dataset was derived from a single institution, and variations in staining protocols, scanner hardware, and image acquisition may affect generalisability across centres [22]. In addition, the projected workload reductions and FTE savings remain theoretical and depend on digital infrastructure, regulatory governance, and the successful integration of AI triage into routine diagnostic pathways. Prospective multi-site validation studies incorporating cost-effectiveness analyses and real-world implementation metrics will therefore be essential before widespread adoption.

Conclusion

Ultimately, the question is not whether artificial intelligence can recognise high-grade dysplasia - our data and prior studies demonstrate that it can - but how it can be integrated safely into routine pathology workflows in a way that improves efficiency without compromising patient care. We envisage a stepwise implementation model beginning with artificial intelligence-assisted case previewing within digital worklists, progressing to real-time diagnostic assistance during sign-out, and eventually enabling supervised automatic sign-out of low-risk, high-volume lesions under structured quality assurance frameworks. This trajectory mirrors the historical evolution of task-sharing roles within pathology and offers a credible pathway toward sustainable diagnostic practice in the era of digital medicine.

References

1. Renshaw AA. Rescreening in cervical cytology for quality control. When bad data is worse than no data, or what works, what doesn't, and why. Clin Lab Med. 2003;23(3):695-708.

2. The Royal College of Pathologists; Institute of Biomedical Science. The role of scientists in histopathology reporting [Internet]. 2023 [cited 2026 Jun 5]. Available from: https://www.rcpath.org/static/30fca2d0-9e82-40be-9c7151ff5969a575/The-role-of-scientists-in-histopathology-reporting-RCPath-and-IBMS-joint-statement-Sept-2023.pdf

3. Deb A, Perisetti A, Goyal H, Aloysius MM, Sachdeva S, Dahiya D, et al. Gastrointestinal endoscopy-associated infections: update on an emerging issue. Dig Dis Sci. 2022;67(5):1718-32.

4. Shaukat A, Wels J, Malhotra A, Greer NL, MacDonald R, Carlyle M, et al. Colonoscopy outcomes by duration of NPO status prior to colonoscopy with moderate or deep sedation. Washington (DC): Department of Veterans Affairs (US); 2015.

5. Shaukat A, Holub J, Pike IM, Pochapin M, Greenwald D, Schmitt C, et al. Benchmarking adenoma detection rates for colonoscopy: results from a US-based registry. Am J Gastroenterol. 2021;116(9):1946-9.

6. Sarvepalli S, Garber A, Rothberg MB, Mankaney G, McMichael J, Morris-Stiff G, et al. Association of adenoma and proximal sessile serrated polyp detection rates with endoscopist characteristics. JAMA Surg. 2019;154(7):627-35.

7. Bretagne JF, Manfredi S, Piette C, Hamonic S, Durand G, Riou F. Yield of high-grade dysplasia based on polyp size detected at colonoscopy: a series of 2295 examinations following a positive fecal occult blood test in a population-based study. Dis Colon Rectum. 2010;53(3):339-45.

8. Tsai FC, Strum WB. Prevalence of advanced adenomas in small and diminutive colon polyps using direct measurement of size. Dig Dis Sci. 2011;56(8):2384-8.

9. McGenity C, Clarke EL, Jennings C, Matthews G, Cartlidge C, Freduah-Agyemang H, et al. Artificial intelligence in digital pathology: a systematic review and meta-analysis of diagnostic test accuracy. NPJ Digit Med. 2024;7(1):114.

10. Shafi S, Parwani AV. Artificial intelligence in diagnostic pathology. Diagn Pathol. 2023;18(1):109.

11. Strum WB. Colorectal adenomas. N Engl J Med. 2016;375(4):387-90.

12. Chetty R, Johnson JE. The management of implementing a digital pathology workflow. Diagn Histopathol. 2023;29(9):420-3.

13. Brodsky V, Ullah E, Bychkov A, Song AH, Walk EE, Louis P, et al. Generative artificial intelligence in anatomic pathology. Arch Pathol Lab Med. 2025;149(4):298-318.

14. Williams DKA Jr, Graifman G, Hussain N, Amiel M, Tran P, Reddy A, et al. Digital pathology, deep learning, and cancer: a narrative review. Transl Cancer Res. 2024;13(5):2544-60.

15. Du X, Hao S, Olsson H, Kartasalo K, Mulliqi N, Rai B, et al. Effectiveness and cost-effectiveness of artificial intelligence-assisted pathology for prostate cancer diagnosis in Sweden: a microsimulation study. Eur Urol Oncol. 2025;8(1):80-6.

16. Chen M, Wang Y, Wang Q, Shi J, Wang H, Ye Z, et al. Impact of human and artificial intelligence collaboration on workload reduction in medical image interpretation. NPJ Digit Med. 2024;7(1):349.

17. Kasim JM. Role of artificial intelligence in fracture liaison service setting. Med Pregl. 2025;78(1-2):7-9.

18. Faghani S, Codipilly DC, Vogelsang D, Moassefi M, Rouzrokh P, Khosravi B, et al. Development of a deep learning model for the histologic diagnosis of dysplasia in Barrett's esophagus. Gastrointest Endosc. 2022;96(6):918-25.e3.

19. Deman F, Broeckx G, Declercq S, Degotte Q, Raymaekers J, Salgado R, et al. Practical implementation of AI in a non-academic, non-commercial pathology laboratory: real world experience and lessons learned. Histopathology. 2025;87(5):635-46.

20. Retamero JA, Gulturk E, Bozkurt A, Liu S, Gorgan M, Moral L, et al. Artificial intelligence helps pathologists increase

diagnostic accuracy and efficiency in the detection of breast cancer lymph node metastases. Am J Surg Pathol. 2024;48(7):846-54.

21. Yilmaz F, Brickman A, Najdawi F, Yakirevich E, Egger R, Resnick MB. Advancing artificial intelligence integration into the pathology workflow: exploring opportunities in gastrointestinal tract biopsies. Lab Invest. 2024;104(5):102043.

22. Fogt F. The illusion of diagnostic agreement: institutional bias as a hidden force in modern medicine. Med Pregl. 2025;78(5-8):127-31.

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BIBLID.0025-8105:(2026):LXXIX:3-6:67-73.

CORRELATION OF LABORATORY, RADIOLOGICAL AND CLINICAL PARAMETERS IN PATIENTS WITH POPLITEAL ARTERY ANEURYSM THROMBOSIS – A CASE-CONTROL STUDY

KORELACIJA LABORATORIJSKIH, RADIOLOŠKIH I KLINIČKIH PARAMETARA KOD PACIJENATA SA TROMBOZOM ANEURIZME ZATKOLENE ARTERIJE – STUDIJA SLUČAJEVA

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Abstract

Introduction. Popliteal artery aneurysm may present with acute thrombosis, a complication associated with limb-threatening ischaemia. This study aimed to identify clinical, radiological, and laboratory features associated with acute popliteal artery aneurysm thrombosis at presentation, rather than to establish causal risk factors for future thrombosis. **Material and Methods.** A case-control study included 142 patients with popliteal artery aneurysm treated at a tertiary vascular surgery centre between January 2017 and December 2024. Cases (n=71) presented with acute thrombosis (Rutherford categories I through IIb); controls (n=71) had asymptomatic popliteal artery aneurysm without thrombosis confirmed by imaging. Demographic, clinical, radiological and laboratory parameters were compared. Multivariable logistic regression identified features independently associated with thrombosis at presentation. **Results.** Patients with thrombosis were older (67.4 versus 61.2 years; p=0.002), more often smokers (73.2% versus 47.9%; p<0.001), and diabetic (43.7% versus 25.4%; p=0.009). Aneurysm diameter was larger (29.3 versus 23.7 millimetres; p<0.001), mural thrombus was more frequent (67.6% versus 29.6%; p<0.001), and D-dimer was higher (1,842 versus 724 nanograms per millilitre; p<0.001). The strongest independent associations were observed for mural thrombus (odds ratio 3.82), aneurysm diameter above 25 millimetres (odds ratio 3.21) and D-dimer above 1,000 nanograms per millilitre (odds ratio 3.14). **Conclusion.** In this single-centre case-control sample, acute popliteal artery aneurysm thrombosis was associated with larger aneurysm diameter, mural thrombus, and elevated D-dimer levels, alongside older age, smoking, and diabetes. Laboratory biomarkers should be interpreted as contemporaneous markers of the acute thrombotic state rather than antecedent predictors. Prospective validation is needed before diagnostic application.

Key words: Popliteal Artery Aneurysm; Thrombosis; Diagnostic Imaging; Signs and Symptoms; Fibrinogen; Biomarkers; Fibrin Fibrinogen Degradation Products

Sažetak

Uvod. Aneurizma poplitealne arterije može se manifestovati akutnom trombozom, komplikacijom povezanom sa ishemijom koja ugrožava ekstremitet. Cilj studije bio je identifikacija kliničkih, radioloških i laboratorijskih karakteristika povezanih sa akutnom trombozom aneurizme poplitealne arterije pri prezentaciji, a ne utvrđivanje kauzalnih faktora rizika za buduću trombozu. **Materijal i metode.** Sprovedena je studija slučajeva i kontrola koja je obuhvatila 142 pacijenta sa aneurizmom poplitealne arterije lečenih u tercijarnom centru za vaskularnu hirurgiju (januar 2017–decembar 2024). Pacijenti su bili slučajevi (n = 71) sa akutnom trombozom (*Rutherford* kategorije I do IIb), kontrole (n = 71) pacijenti sa asimptomatskom aneurizmom bez tromboze potvrđenom imidžingom. Poređeni su demografski, klinički, radiološki i laboratorijski parametri. Multivarijantnom logističkom regresijom identifikovane su karakteristike nezavisno povezane sa trombozom pri prezentaciji. **Rezultati.** Pacijenti sa trombozom bili su stariji (67,4 naspram 61,2 godine; p = 0,002), češće pušači (73,2% naspram 47,9%; p < 0,001) i imali su dijabetes (43,7% naspram 25,4%; p = 0,009). Dijametar aneurizme bio je veći (29,3 naspram 23,7 milimetara; p < 0,001), muralni tromb češći (67,6% naspram 29,6%; p < 0,001), D-dimer viši (1.842 naspram 724 nanograma po mililitru; p < 0,001). Najsnažnije nezavisne asocijacije uočene su za muralni tromb (odnos šansi 3,82), dijametar iznad 25 milimetara (odnos šansi 3,21) i D-dimer iznad 1.000 nanograma po mililitru (odnos šansi 3,14). **Zaključak.** U ovom jednocentričnom uzorku, akutna tromboza aneurizme poplitealne arterije bila je povezana sa većim dijametrom aneurizme, prisustvom muralnog tromba i povišenim D-dimerom, uz stariju životnu dob, pušenje i dijabetes.

Ključne reči: aneurizma poplitealne arterije; tromboza; dijagnostički imidžing; znaci i simptomi: fibrinogen; biomarkeri; produkti razgradnje fibrina i fibrinogena

Introduction

Popliteal artery aneurysm (PAA) is the most common peripheral arterial aneurysm and may present with acute thrombosis, a complication that can lead to limb-threatening ischaemia [1,2]. The prevalence of PAA in the general population is approximately 1%, with a strong male predominance and higher in-

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Abbreviations

PAA – popliteal artery aneurysm
CTA – computed tomography angiography
IQR – interquartile range
OR – odds ratio
CI – confidence interval
AUC – area under the receiver operating characteristic curve
VIF – variance inflation factor
SD – standard deviation
FEU – fibrinogen equivalent units
EPV – events per variable

cidence among older patients with cardiovascular comorbidities [3]. Bilateral PAAs are present in 50–70% of cases, and associated abdominal aortic aneurysms are found in 40–50% of patients [4].

Acute thrombosis of PAA is a limb-threatening emergency; in a systematic review of 895 cases, the early amputation rate reached 14% [5]. Unlike abdominal aortic aneurysms, which primarily present with rupture, PAAs more commonly thrombose due to altered haemodynamics and intraluminal thrombus accumulation [6]. Current Society for Vascular Surgery guidelines recommend elective repair for symptomatic aneurysms of any size and for asymptomatic aneurysms exceeding 20 mm in diameter or containing mural thrombus [7].

Risk stratification for PAA thrombosis has traditionally focused on aneurysm size and morphological features. However, morphology-only assessment may miss systemic prothrombotic signals [8]. Several biomarkers, particularly D-dimer and fibrinogen, have been linked to adverse cardiovascular outcomes in peripheral arterial disease [9,10], and hypoalbuminaemia has been associated with poor results after vascular surgery [11,12]. A recent multicentre study also suggested that per cent thrombus burden may be more informative than diameter alone in identifying high-risk PAAs [13].

Previous reports on PAA thrombosis have focused on morphological correlates and surgical outcomes [8,9], with limited attention to laboratory biomarkers measured at the time of acute presentation. The study aimed to identify clinical, radiological, and laboratory features associated with acute PAA thrombosis at presentation, rather than to establish causal risk factors for future thrombosis.

Material and Methods

Study design and setting

This case-control study was conducted at a tertiary referral centre for vascular emergencies serving a population of approximately 2 million. Data were collected from patients treated between January 2017 and December 2024. The study was approved by the Institutional Ethics Committee (approval number: 00-20/522) and conducted in accordance with the Declaration of Helsinki. The need for individual informed consent was waived due to the study's retrospective design. This report follows STROBE recommendations for case-control studies [14]. A completed STROBE checklist is provided as Supplementary Table S1.

Participants

Of 180 patients diagnosed with PAA during the study period, 142 were included in the final analysis **(Figure 1).** Thirty-eight patients were excluded: incomplete clinical or laboratory data (n=22; predominantly missing D-dimer in 14 and albumin in 11, with some patients missing both), previous ipsilateral revascularisation (n=8), active malignancy (n=5), and current anticoagulation therapy (n=3). Exclusion reasons were mutually exclusive (primary reason assigned). Characteristics of included and excluded patients were compared; no significant differences in age, sex, or aneurysm diameter were observed (all $p>0.10$).

Cases (n=71) were patients presenting with acute PAA thrombosis confirmed by computed tomography angiography (CTA) or duplex ultrasonography, defined as complete occlusion of the popliteal artery

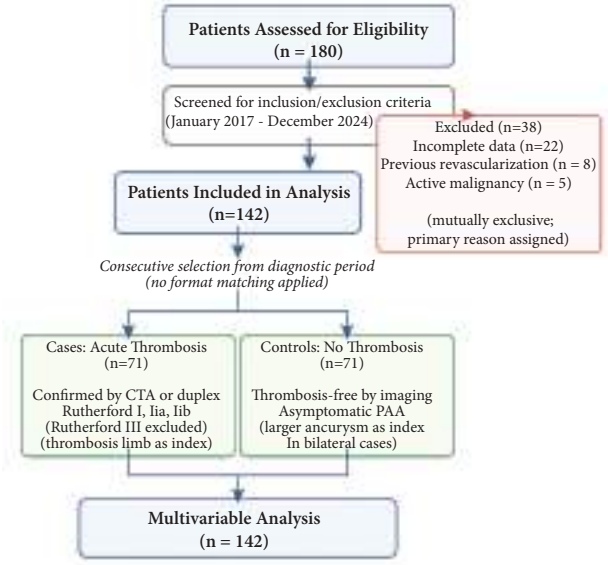

Figure 1. Patient selection flow diagram. Of 180 patients with popliteal artery aneurysm assessed for eligibility, 142 were included (71 cases with acute thrombosis, 71 asymptomatic controls confirmed to be thrombosis-free by imaging). Exclusion reasons are mutually exclusive (primary reason assigned). In bilateral cases, the thrombosed limb was analysed, and the larger aneurysm in controls. Cases included Rutherford categories I, IIa and IIb [19]; Rutherford III was excluded.

within the aneurysmal segment with clinical signs of acute limb ischaemia (Rutherford categories I, IIa and IIb) [19]. Patients with irreversible ischaemia (Rutherford III) were excluded. Controls (n=71) were patients with asymptomatic PAA diagnosed during the same period and confirmed to be thrombosis-free by imaging. Controls were selected consecutively from the institutional database at a 1:1 ratio without formal matching. In patients with bilateral PAAs, the thrombosed limb was analysed in cases, whereas the larger aneurysm was used as the index lesion in controls.

Variables analysed

Demographic data included age and sex. Clinical variables included smoking status (current or former smoker versus never smoker; categories combined owing to similar vascular risk profiles), diabetes mellitus, hypertension and dyslipidaemia. Radiological parameters were obtained from CTA (primary modality, n=118; 83%) or duplex ultrasonography (n=24; 17%). The distribution of imaging modalities was similar between groups (CTA: cases 82%, controls 85%). Parameters assessed included maximum outer-to-outer aneurysm diameter, presence of bilateral PAA, presence of mural thrombus in the aneurysm sac, and infrapopliteal arterial stenosis (defined as >50% stenosis in any tibial artery, assessed by diameter reduction on CTA or peak systolic velocity ratio >2.5 on duplex). Radiologists were blinded to laboratory results and the study hypothesis. Inter-observer agreement for mural thrombus detection was substantial ($\kappa = 0.78$).

Laboratory biomarkers included D-dimer (ng/mL, fibrinogen equivalent units, immunoturbidimetric assay), fibrinogen (g/L, Clauss method) and serum albumin (g/dL). Laboratory samples were obtained within 6 hours of emergency department presentation (cases) or at outpatient diagnostic workup (controls), prior to therapeutic anticoagulation or thrombolysis. This difference in sampling context is an inherent limitation of the case-control design and is addressed in the Discussion.

Statistical analysis

Distributional assumptions for continuous variables were assessed using visual inspection of histograms and Q-Q plots, supplemented by the Shapiro-Wilk test. Normally distributed variables were presented as mean ± standard deviation (SD) and compared using Student's t-test. Non-normally distributed variables were presented as medians with interquartile ranges (IQRs) and compared using the Mann-Whitney U test. Categorical variables were presented as absolute and relative frequencies and compared using the chi-square test; Fisher's exact test was used when expected cell counts were below 5. Univariable comparisons were considered exploratory and were interpreted primarily to describe between-group differences rather than to establish independent effects. Given this exploratory nature, no formal correction for multiple testing was applied, and univariable p-values are interpreted descriptively.

Continuous variables were dichotomised using clinically established cut-off values (age >65 years, aneurysm diameter >25 mm, D-dimer >1000 ng/mL, fibrinogen >4 g/L, albumin <3.5 g/dL) to facilitate clinical interpretability. This simplified interpretation may have reduced statistical power and obscured non-linear associations. The 25 mm diameter threshold was chosen to optimise separation in this dataset while retaining clinical relevance; guideline thresholds for elective repair (e.g. 20 mm) address a different clinical decision context.

A complete case analysis was performed. Multiple imputation was not used; the potential impact of missing data is discussed in the Limitations section. Candidate variables were entered into multivariable logistic regression based on clinical relevance. Multicollinearity was assessed using variance inflation factors (VIF); all values were <2.5. Results were reported as odds ratios (OR) with 95% confidence intervals (CI). To assess model discrimination, the area under the receiver operating characteristic curve (AUC) was calculated, with internal validation by bootstrap resampling (1,000 iterations) and 10-fold cross-validation. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test, the calibration-in-the-large intercept, the calibration slope and the Brier score. Given the limited number of events relative to predictors (an events-per-variable ratio of approximately 8), the multivariable model should be considered exploratory and hypothesis-generating, despite internal resampling procedures. No formal a priori sample size calculation was performed; the number of candidate variables was constrained by the available number of cases. Statistical significance was set at $p<0.05$. Analyses were performed using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria) with packages 'rms' and 'pROC'.

Results

Demographic and clinical characteristics

Baseline demographic and clinical characteristics are presented in **Table 1**. Mean age in the acute thrombosis group was 67.4±9.2 years compared to 61.2±8.4 years in controls (p=0.002; mean difference 6.2 years, 95% CI 2.3–10.1). The proportion of patients older than 65 years was higher in the thrombosis

Table 1. Demographic and clinical characteristics of the study groups

Variable	Acute thrombosis (n=71)	Control (n=71)	p
Age (years, mean±SD)	67.4 ± 9.2	61.2 ± 8.4	0.002
Age >65 years, n (%)	46 (64.8)	31 (43.7)	0.012
Male sex, n (%)	63 (88.7)	58 (81.7)	0.271
Smoking*, n (%)	52 (73.2)	34 (47.9)	<0.001
Diabetes mellitus, n (%)	31 (43.7)	18 (25.4)	0.009
Hypertension, n (%)	45 (63.4)	39 (54.9)	0.291
Dyslipidaemia, n (%)	38 (53.5)	30 (42.3)	0.127

SD – standard deviation. *Smoking defined as current or former smoker versus never smoker; current and former smokers were combined due to similar vascular risk profiles

Table 2. Radiological characteristics of the study groups

Variable	Acute thrombosis (n=71)	Control (n=71)	p
Max. diameter* (mm, mean±SD)	29.3 ± 4.5	23.7 ± 3.9	<0.001
Diameter >25 mm, n (%)	54 (76.1)	28 (39.4)	<0.001
Bilateral PAA, n (%)	29 (40.8)	14 (19.7)	0.014
Mural thrombus, n (%)	48 (67.6)	21 (29.6)	<0.001
Infrapopliteal stenosis >50%†, n (%)	27 (38.0)	13 (18.3)	0.008

PAA – popliteal artery aneurysm; SD – standard deviation. *Maximum outer-to-outer diameter measured by CTA or duplex. †Defined as >50% stenosis in any tibial artery

group (64.8% vs 43.7%; p=0.012). Most patients were male (88.7% vs 81.7%; p=0.271). Smoking was more prevalent among cases (73.2% vs 47.9%; p<0.001), as was diabetes mellitus (43.7% vs 25.4%; p=0.009). Hypertension and dyslipidaemia did not differ significantly between groups.

Among 71 cases, Rutherford category distribution was: category I (n=17, 23.9%), category IIa (n=38, 53.5%), and category IIb (n=16, 22.5%). Median time from symptom onset to presentation was 18 hours (IQR 8–36).

Radiological characteristics

Radiological characteristics are presented in **Table 2.** Mean maximum aneurysm diameter was larger in the thrombosis group (29.3±4.5 mm vs 23.7±3.9 mm; p<0.001; mean difference 5.6 mm, 95% CI 4.2–7.0). Diameter above 25 mm was observed in 76.1% of cases versus 39.4% of controls (p<0.001). Bilateral PAA was present in 40.8% of cases compared to 19.7% of controls (p=0.014). Mural thrombus was strongly associated with acute thrombosis (67.6% vs 29.6%; p<0.001). Infrapopliteal stenosis >50% was more prevalent among cases (38.0% vs 18.3%; p=0.008).

Laboratory characteristics

Laboratory findings are presented in **Table 3.** Median D-dimer was higher in the thrombosis group (1842 ng/mL, IQR 876–3214) than in controls (724 ng/mL, IQR 412–1156; p<0.001). D-dimer above 1000 ng/mL was present in 59.1% of cases versus 26.8% of controls (p<0.001). Median fibrinogen was 4.2 g/L (IQR 3.4–5.1) in cases versus 3.5 g/L (IQR 2.9–4.2) in controls (p<0.001). Hypoalbuminaemia (albumin <3.5 g/dL) was more frequent in cases (40.8% vs 16.9%; p=0.004).

Table 3. Laboratory characteristics of the study groups

Variable	Acute thrombosis (n=71)	Control (n=71)	p
D-dimer (ng/mL FEU), median (IQR)	1842 (876–3214)	724 (412–1156)	<0.001
D-dimer >1000 ng/mL, n (%)	42 (59.1)	19 (26.8)	<0.001
Fibrinogen (g/L, Clauss), median (IQR)	4.2 (3.4–5.1)	3.5 (2.9–4.2)	<0.001
Fibrinogen >4 g/L, n (%)	33 (46.5)	17 (23.9)	0.002
Albumin (g/dL), median (IQR)	3.4 (3.1–3.8)	3.9 (3.6–4.2)	<0.001
Albumin <3.5 g/dL, n (%)	29 (40.8)	12 (16.9)	0.004

IQR – interquartile range; FEU – fibrinogen equivalent units. Laboratory samples: cases within 6 h of emergency presentation; controls at outpatient workup

Table 4. Multivariable logistic regression: features independently associated with acute PAA thrombosis at presentation

Variable	OR (95% CI)	β (SE)	VIF	p
Age >65 years	2.31 (1.24–4.32)	0.84 (0.31)	1.12	0.008
Smoking	2.58 (1.41–4.72)	0.95 (0.30)	1.18	0.002
Diabetes mellitus	2.14 (1.18–3.88)	0.76 (0.30)	1.08	0.012
Diameter >25 mm	3.21 (1.76–5.87)	1.17 (0.31)	1.24	<0.001
Mural thrombus	3.82 (2.04–7.14)	1.34 (0.32)	1.31	<0.001
Infrapopliteal stenosis >50%	2.42 (1.28–4.58)	0.88 (0.32)	1.15	0.006
D-dimer >1000 ng/mL	3.14 (1.68–5.87)	1.14 (0.32)	1.42	<0.001
Fibrinogen >4 g/L	2.48 (1.32–4.66)	0.91 (0.32)	1.38	0.005
Albumin <3.5 g/dL	2.76 (1.44–5.29)	1.02 (0.33)	1.21	0.002

OR – odds ratio; CI – confidence interval; β – regression coefficient; SE – standard error; VIF – variance inflation factor. Model intercept $\beta_0 = -4.21$ (verified for this dataset; identical to the logistic model fitted on the same 142-patient sample). Apparent AUC = 0.89 (95% CI 0.84–0.93); optimism-corrected AUC (1,000 bootstrap) = 0.87; optimism = 0.02. Hosmer-Lemeshow $\chi^2 = 9.4$, p = 0.21. Calibration-in-the-large intercept = −0.08; calibration slope = 0.91. Brier score = 0.14. Because of 1:1 case-control sampling, the intercept and absolute probabilities are sample-dependent and not transportable to populations with different thrombosis prevalence. The model is exploratory.

Multivariable analysis

Multivariable logistic regression results are presented in **Table 4.** Nine variables were independently associated with acute thrombosis at presentation. The strongest associations were observed for mural thrombus (OR 3.82; 95% CI 2.04–7.14; p<0.001), aneurysm diameter >25 mm (OR 3.21; 95% CI 1.76–5.87; p<0.001), and D-dimer >1000 ng/mL (OR 3.14; 95% CI 1.68–5.87; p<0.001). Smoking (OR 2.58), hypoalbuminaemia (OR 2.76), infrapopliteal stenosis >50% (OR 2.42), elevated fibrinogen (OR 2.48), diabetes (OR 2.14) and age >65 years (OR 2.31) were also independently associated. All VIF values were below 2.5.

D-dimer and fibrinogen showed moderate correlation (Spearman r = 0.41), as reflected in their VIF values of 1.42 and 1.38; both were retained, as they capture partially distinct aspects of the coagulation cascade, in which an imbalance between procoagulant and inhibitory components of haemostasis underlies the prothrombotic state [20].

Exploratory assessment of model discrimination yielded an apparent AUC of 0.89 (95% CI 0.84–0.93). Bootstrap internal validation (1,000 iterations) produced an optimism-corrected AUC of 0.87 (95% CI 0.82–0.91), and 10-fold cross-validation yielded a mean AUC of 0.86. Bootstrap correction revealed an optimism of 0.02 (apparent AUC 0.89 minus corrected AUC 0.87), which, although modest in absolute terms, should be interpreted in the context of a low events-per-variable ratio of approximately 8. The Hosmer-Lemeshow goodness-of-fit test was non-significant (χ^2=9.4; p=0.21). Calibration-in-the-large intercept was −0.08, and calibration slope was 0.91, suggesting adequate calibration within this case-control sample. The Brier score was 0.14.

Discussion

In this case-control study of 142 patients with PAA, we identified clinical, radiological and laboratory features associated with acute thrombosis at presentation. Multivariable analysis revealed nine independently associated variables, with mural thrombus, larger aneurysm diameter, and elevated D-dimer showing the strongest associations.

Our findings are consistent with previous reports linking aneurysm size and mural thrombus to PAA complications [8,9]. Martelli et al. found that superficial femoral artery occlusion and poor distal runoff were independently associated with PAA thrombosis [9]. We used infrapopliteal stenosis >50% as a simplified measure; this is not equivalent to formal runoff scores but captures clinically relevant distal disease. A recent multicentre study by Bellomo et al. suggested that per cent thrombus burden may be more informative than diameter alone for identifying high-risk PAAs [13]; this is consistent with our finding that mural thrombus carried the strongest association (OR 3.82), although whether thrombus quantity adds incremental value over its mere presence remains to be tested prospectively.

An additional aspect of this study is the inclusion of laboratory biomarkers measured at presentation, alongside clinical and imaging variables. The association between D-dimer and thrombotic events in peripheral arterial disease is well supported. Kremers et al., in a systematic review of over 21,000 patients, found that elevated D-dimer and fibrinogen were associated with increased mortality [10]. Vidula et al. reported that D-dimer levels were independently associated with near-term mortality in peripheral arterial disease [11]. However, these studies addressed general peripheral arterial disease populations rather

than PAA specifically; caution is warranted when extrapolating to acute PAA thrombosis.

Hypoalbuminaemia was independently associated with thrombosis in our study (OR 2.76), consistent with literature linking low albumin to adverse vascular outcomes [12,15]. Hypoalbuminaemia may contribute through reduced antithrombin-binding capacity, impaired nitric oxide transport, and heightened platelet aggregation, and may also reflect chronic nutritional depletion and systemic inflammation [16].

D-dimer, fibrinogen, and albumin should be interpreted primarily as contemporaneous markers associated with the acute thrombotic state at presentation, rather than antecedent predictors of future thrombosis in asymptomatic aneurysms. Laboratory samples in cases were obtained during the acute event, whereas controls were sampled during outpatient workup. This fundamental difference in sampling context means that the observed laboratory differences may partly reflect the acute-phase response to thrombosis itself (reverse causality) rather than pre-existing risk. Had pre-thrombotic laboratory values been available, the magnitude of the D-dimer and fibrinogen associations would likely be substantially attenuated, and the model's discrimination would decrease accordingly.

Several limitations warrant consideration. The comparison of clinically extreme phenotypes (acute thrombosis versus asymptomatic aneurysm) reflects spectrum bias inherent in the study design, inflating discrimination metrics and limiting applicability to intermediate clinical presentations. In real-world emergency triage, the diagnostic challenge often involves distinguishing acute PAA thrombosis from other causes of acute limb ischaemia or from symptomatic but non-thrombosed PAA. Controls were selected consecutively without age or sex matching; the 6.2-year age difference between groups may confound univariable comparisons, although age was included in the multivariable model. Because of the 1:1 case-control sampling scheme, the model intercept and implied absolute probabilities are sample-dependent and should not be transported directly to populations with different thrombosis prevalence.

The study is single-centre and has a relatively small sample size, yielding an events-per-variable ratio of approximately 8, which increases the risk of overfitting despite bootstrap correction. That all nine candidate variables reached conventional significance in a model with this EPV ratio warrants cautious interpretation; the possibility of unstable coefficient estimates cannot be excluded. Of 180 patients, 22 (12.2%) were excluded due to incomplete data, predominantly missing D-dimer (n=14) and albumin (n=11); multiple imputation was not performed, which may have introduced selection bias. Dichotomisation of continuous variables simplified interpretation but may have reduced statistical power and obscured non-linear associations. Radiological parameters were obtained by CTA (83%) or duplex ultrasonography (17%), introducing potential measurement heterogeneity; a sensitivity analysis restricted to the CTA subgroup would be informative but was not performed owing to sample size constraints. Finally, the 8-year study period implies potential evolution of diagnostic practices. The fibrinogen and D-dimer elevations we observed are consistent with earlier work linking these markers to arterial thrombotic events and to the severity of peripheral arterial disease [17,18]. Most cases in our cohort presented with advanced ischaemia (Rutherford categories IIa or IIb) [19], reflecting the emergent nature of acute popliteal artery aneurysm thrombosis. Because inherited and acquired thrombophilia contribute to arterial thrombotic events [20], the biomarker changes observed at presentation should be regarded as part of this acute thrombotic process rather than as isolated diagnostic signals.

Conclusion

In this single-centre case-control sample, acute popliteal artery aneurysm thrombosis was associated with older age, smoking, diabetes, larger aneurysm diameter, mural thrombus, and higher D-dimer and fibrinogen with lower serum albumin at presentation. Mural thrombus, aneurysm diameter above 25 mm, and D-dimer above 1000 ng/mL showed the strongest independent associations. The observed laboratory differences may support diagnostic recognition of acute thrombosis at presentation, but they should not be interpreted as validated prognostic markers for future thrombosis. These associations describe the presentation profile of acutely thrombosed popliteal artery aneurysm in this cohort but require prospective validation in independent cohorts before any diagnostic use.

References

1. Cervin A, Wanhainen A, Bjorck M. Popliteal aneurysm repair: open versus endovascular surgery. Semin Vasc Surg. 2019; 32(3-4):148-57.

2. Trinidad-Hernandez M, Ricotta JJ 2nd, Gloviczki P, Kalra M, Oderich GS, Duncan AA, et al. Results of elective and emergency endovascular repairs of popliteal artery aneurysms. J Vasc Surg. 2013;57(5):1299-305.

3. Lawrence PF, Lorenzo-Rivero S, Lyon JL. The incidence of iliac, femoral, and popliteal artery aneurysms in hospitalized patients. J Vasc Surg. 1995;22(4):409-16.

4. Trickett JP, Scott RA, Tilney HS. Screening and management of asymptomatic popliteal aneurysms. J Med Screen. 2002; 9(2):92-3.

5. Kropman RH, Schrijver AM, Kelder JC, Moll FL, de Vries JP. Clinical outcome of acute leg ischaemia due to thrombosed popliteal artery aneurysm: systematic review of 895 cases. Eur J Vasc Endovasc Surg. 2010;39(4):452-7.

6. Dawson I, Sie RB, van Bockel JH. Atherosclerotic popliteal aneurysm. Br J Surg. 1997;84(3):293-9.

7. Farber A, Angle N, Avgerinos E, Dubois L, Eslami M, Geraghty P, et al. The Society for Vascular Surgery clinical practice guidelines on popliteal artery aneurysms. J Vasc Surg. 2022;75(1 Suppl):109S-20.

8. Pulli R, Dorigo W, Castelli P, Dorrucci V, Ferilli F, De Blasis G, et al. A multicentric experience with open surgical repair and endovascular exclusion of popliteal artery aneurysms. Eur J Vasc Endovasc Surg. 2013;45(4):357-63.

9. Martelli E, Ippoliti A, Ventoruzzo G, De Vivo G, Ascoli Marchetti A, Pistolese GR. Popliteal artery aneurysms. Factors associated with thromboembolism and graft failure. Int Angiol. 2004;23(1):54-65.

10. Kremers B, Wübbeke L, Mees B, Ten Cate H, Spronk H, Ten Cate-Hoek A. Plasma biomarkers to predict cardiovascular outcome in patients with peripheral artery disease: a systematic review and meta-analysis. Arterioscler Thromb Vasc Biol. 2020;40(9):2018-32.

11. Vidula H, Tian L, Liu K, Criqui MH, Ferrucci L, Pearce WH, et al. Biomarkers of inflammation and thrombosis as predictors of near-term mortality in patients with peripheral arterial disease: a cohort study. Ann Intern Med. 2008;148(2):85-93.

12. Gibbs J, Cull W, Henderson W, Daley J, Hur K, Khuri SF. Preoperative serum albumin level as a predictor of operative mortality and morbidity. Arch Surg. 1999;134(1):36-42.

13. Bellomo TR, Goudot G, Lella SK, Gaston B, Sumetsky N, Patel S, et al. Percent thrombus predicts popliteal artery aneurysm related limb threatening events. Ann Surg. 2025;282(6):1134-9.

14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007; 147(8):573-7.

15. Valeriani E, Pannunzio A, Palumbo IM, Bartimoccia S, Cammisotto V, Castellani V, et al. Risk of venous thromboembolism and arterial events in patients with hypoalbuminemia: a comprehensive meta-analysis of more than 2 million patients. J Thromb Haemost. 2024;22(10):2823-33.

16. Bath J, Smith JB, Woodard J, Kruse RL, Vogel TR. Complex relationship between low albumin level and poor outcome after lower extremity procedures for peripheral artery disease. J Vasc Surg. 2021;73(1):200-9.

17. Lowe GD, Rumley A. Use of fibrinogen and fibrin D-dimer in prediction of arterial thrombotic events. Thromb Haemost. 1999;82(2):667-72.

18. Lee AJ, Fowkes FG, Lowe GD, Rumley A. Fibrin D-dimer, haemostatic factors and peripheral arterial disease. Thromb Haemost. 1995;74(3):828-32.

19. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26(3):517-38.

20. Obradović D. Trombofilija i tromboza (Thrombophilia and thrombosis). Med Pregl. 2005;58(7-8):368-74.

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TIMING OF SURGERY INFLUENCES THE RESULT OF ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

VREME OPERACIJE UTIČE NA REZULTAT REKONSTRUKCIJE PREDNJEG UKRŠTENOG LIGAMENTA

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Abstract

Introduction. The study aimed to determine whether delaying reconstruction of the anterior cruciate ligament significantly affects return to sporting activity, surgical outcomes, and rates of associated knee injuries, and to identify reasons for delay. **Material and Methods.** The study included 1,020 patients of both sexes (80% men and 20% women); 67% were recreational athletes, and 51% were footballers. All patients filled out a questionnaire, which contained functional activity scales. Patients were divided into an early-operated group (n = 320, surgery between 3 weeks and 3 months after injury) and a delayed-operated group (n =700, surgery more than 3 months after injury). **Results and Discussion.** The mean preoperative Tegner score was 4.49, and the postoperative score was 5.72. The mean preoperative Lysholm score was 73.28, rising to 92.08 postoperatively. The longer the interval before diagnosis, surgery, and resumption of running, training and competing, the lower the resulting activity scores. Early reconstructions were associated with higher mean postoperative scores than delayed reconstruction on both the Tegner scale (6.2 vs 5.5) and the Lysholm scale (93.1 vs 91.6). The early-operated group also had a lower rate of medial meniscal injury (20% vs 26%), and less cartilage damage (12.2% vs 22.3%). Patients' own (subjective) reasons accounted for 61% of delays. **Conclusion.** The ideal timing for reconstruction is patient-specific and depends on resolution of swelling and restoration of knee range of motion and muscle strength. Delaying surgery beyond 3 months is associated with secondary injury to the medial meniscus and cartilage, and with poorer functional and sporting outcomes.
Key words: Anterior Cruciate Ligament Reconstruction; Treatment Outcome; Prognosis; Time Factors; Lysholm Knee Score

Sažetak

Uvod. Cilj studije predstavlja utvrđivanje da li odlaganje rekonstrukcije prednjeg ukrštenog ligamenta značajno utiče na: povratak sportskim aktivnostima, rezultat operacije, udružene povrede kolena i analizira razloge za odlaganje operacija. **Materijal i metode.** U uzorku dominiraju: 80% muškaraca, 67% rekreativnih sportista i 51% fudbalera. Svih 1.020 operativno lečenih pacijenata kost–tetiva–kost metodom preoperativno i 12 meseci postoperativno popunjavali su upitnik, koji je sadržao funkcionalne skale aktivnosti. Podelili smo ih u grupu 320 rano operisanih: između tri nedelje i tri meseca nakon povrede (prosečno 2,2 meseca) i grupu 700 odloženo operisanih (više od tri meseca, prosečno 14,8 meseci). **Rezultati i diskusija.** Ukupan prosečni Tegnerov skor (*Tegner*) pre operacije iznosi 4,49, a postoperativni 5,72. Prosečan preoperativni Lišolmov skor (*Lysholm*) je 73,38, a postoperativni 92,08. Što duži period vremena protekne do postavljanja dijagnoze, početka trčanja, treniranja i takmičenja, niže su vrednosti bodovnih skala. Rane rekonstrukcije imaju više prosečne postoperativne vrednosti od kasnih po pitanju Tegner skora (6,2 naspram 5,5), kao i Lišolmove skale (93,1 naspram 91,6). Rano operisana grupa ima manju učestalost povreda unutrašnjeg meniskusa (20% naspram 26%), kao i ređa oštećenja hrskavice (12,2% naspram 22,3%). Subjektivni razlozi pacijenata uzrok su odlaganja operacije u 61% slučajeva. **Zaključak.** Idealno vreme za rekonstrukciju prednjeg ukrštenog ligamenta je individualno i uslovljeno smanjenjem otoka i postizanjem zadovoljavajućeg preoperativnog obima pokreta kolena i mišićne snage. Odlaganje operacije duže od tri meseca nakon povrede dovodi do sekundarnih povreda unutrašnjeg meniskusa i hrskavice, kao i lošijeg nivoa životnih i sportskih aktivnosti.
Ključne reči: rekonstrukcija prednjeg ukrštenog ligamenta; ishod lečenja; prognoza; vremenski factor; Lisholm skor

Introduction

Reconstruction of the anterior cruciate ligament improves quality of life and allows a return to sporting activity [1–3]. Even so, fewer than half of patients (only 28-55%) return to their previous level of sporting activity 1 year after surgery [4–6].

Athletes, sports clubs and the health system often press for early diagnosis and surgery, raising the question whether this haste leads to worse outcomes in

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Abbreviations

ACL – anterior cruciate ligament
BPTB – bone-patellar tendon-bone
HT – hamstring tendons
BMI – body mass index

terms of pain, instability, complications, re-operations and delayed return to unrestricted activity [6–8].

In Canada, the average interval from injury to surgery is 9.5-11.5 months [7], whereas in the United States this interval is considerably shorter, at 3-5 months [8], as is the case in Scandinavian countries, at around 5 months [5].

In the absence of consensus on the ideal timing for surgery, this study aimed to determine the waiting time for surgery in our population, whether the interval between injury and ACL reconstruction affects the rate of associated injury and the surgical outcome (as measured by activity scores), and the reasons for delayed surgery in our sample.

Material and Methods

This multicentre study was conducted at the Clinic for Orthopaedic Surgery and Traumatology, Clinical Center of Vojvodina, in Novi Sad, and at the Department of Orthopaedic Surgery and Traumatology, Subotica General Hospital. It was designed as a descriptive, retrospective study, and was approved by the Ethics Committee of the Clinical Center of Vojvodina.

We surveyed 1020 respondents with ACL injury who underwent surgery between 1 January 2010 and 31 January 2019. To minimise variability arising from surgeon or technique, all patients were operated on by one of two surgeons (with around 6,000 and more than 500 prior surgeries, respectively), working at different institutions, using bone-patellar-tendon-bone (BPTB) graft [9] fixed with interference titanium screws, followed by an identical rehabilitation protocol [10].

Before surgery and 1 year after, patients completed a questionnaire covering circumstances of the injury, subjective complaints, and current knee function [11]. Data recorded for all patients included: age, sex, level of sporting activity; time intervals from injury to diagnosis, from injury to surgery, from surgery to resumption of running, training and competition.

The Tegner activity scale [12] ranges from 0 to 10. A score of 10 denotes competitive sports such as football at national and international level; 9, competitive sports at high intensity (e.g. lower league football, ice hockey, wrestling, gymnastics); 8, high recreational and competitive lower intensity sports (e.g. badminton, athletics [jumping], downhill skiing); 7, frequent recreational (e.g. football, squash, cross-country track) and competitive (e.g. tennis, athletics [running], motocross, handball); 6, recreational sports (e.g. tennis, badminton, handball, basketball, downhill skiing, jogging at least five times a week); 5, recreational (e.g. jogging at least two times a week on uneven ground), work (e.g. heavy labour, forestry), competitive (e.g. cycling, cross-country skiing); 4, recreational (e.g. cycling, cross-country skiing, jogging at least two times a week on even ground), work (e.g. moderately heavy physical work such as housework); 3, competitive and recreational sports (e.g. swimming, walking in rough forest terrain), work (e.g. light labour); 2, work (e.g. light physical work, walking on uneven ground); 1, work (e.g. walking on even ground, sedentary work); 0, disability due to knee problems.

On the Lysholm scale [13], a maximum 100 points are available: instability and pain together account for half of the total score (0-25 points each), with further points allocated for blocking/locking of movement (0-15), swelling (0-10), stairs climbing (0-10), and support, walking and squatting (up to 5 points each).

Patients were divided into two groups: an early-operated group of 320 patients who underwent surgery between 3 weeks and 3 months after the injury, and a delayed-operated group of 700 patients who underwent surgery more than 3 months after injury. We assessed the effect of surgical timing on associated meniscal and cartilage injuries using repeat clinical examination and on functional outcomes using the Tegner and Lysholm scales.

Associated meniscal and cartilage injuries were identified from operative records and compared between groups.

700 patients for whom time from injury to surgery was longer than 3 months were asked to identify the single most important reason for delay. The reasons offered were: a) broadly subjective factors (e.g. the end of a sporting career, fear of surgery [pain, infection and other complications], fear of surgery failure [e.g. continued knee dysfunction], educational commitments [high school or university], family commitments [e.g. pregnancy, childcare], occupational commitments [e.g. inability to take extended leave], voluntary delay in seeking an initial orthopaedic assessment, or other/unknown reasons); b) objective factors, such as excessively long waiting lists and delayed referral for MRI (and thus delayed diagnosis).

Our sample comprised 815 men (79.9%) and 205 women (20.1%). The youngest patient at the time of surgery was 15 years old, and the oldest was 56 years old; the mean age was 27.2 years. Preoperative body mass ranged from 49 kg to 176 kg, and height from 147 cm to 207 cm. Mean height was 179.6 cm in the early-operated group and 181.2 cm in the delayed-operated group. Mean body mass index (BMI) was 24.6 and was

Table 1. Associated injuries in groups of early and late operated patients

	Early surgery (N 320)	Delayed surgery (N 700)	Total (N 1020)
Medial meniscus	64 (20%)	182 (26%)	246 (24.1%)
Lateral meniscus	46 (14.4%)	107 (15.3%)	153 (15%)
Chondral lesion (grade III/IV)	39 (12.2%)	156 (22.3%)	195 (19.1%)

higher in men (25.21) than in women (22.26). Mean body mass was 80.5 kg in the early-operated group and 81.6 kg in the delayed-operated group.

Injury occurred during sporting activities in 985 patients (96.6%); the remaining 35 injuries occurred during road traffic accidents, at work, or during everyday activities. The most common causative sport was football (n = 519; 50.9%), followed by basketball (n = 174; 17.1%), handball (n = 102; 10%), martial arts (n = 61; 6%), skiing (n = 35; 3.4%), and volleyball (n = 33; 3.2%). Other sports, including American football (rugby), tennis, athletics and gymnastics, accounted for the remaining injuries (n = 61; 6%).

Most patients were recreational athletes (n = 679; 66.6%), with professional athletes (n = 306; 30%) competing at international, national, or regional level, and only (n =35; 3.4%) patients reported no sporting activities.

Data were analysed using IBM SPSS Statistics v. 23 and Microsoft Excel 2013. Numerical variables are presented as minimum, maximum, mean and standard deviation; categorical variables are presented as absolute and relative frequencies. Non-parametric methods were used throughout; correlations between numerical variables were assessed using Spearman's rank correlation, and categorical variables were compared using the χ^2 test. Statistical significance was set at $p<0.05$.

Exclusion criteria were: age under 15 years (as our institutions do not treat patients younger than 15 years); previous knee injury, surgery or re-operations; incomplete or unreturned questionnaires; and failure to complete rehabilitation.

Results

Across the whole sample, the mean interval from injury to surgery was 10.6 months. In the early-operated group, the mean interval from injury to diagnosis was under one month (28.6 days), and surgery was performed within 3 months of injury (mean 2.2 months). In the delayed-operated group, the mean interval from injury to surgery was 14.8 months, comprising 8.5 months of waiting for diagnosis and 6.3 months waiting for surgery.

Among the 700 patients who waited more than 3 months for surgery, the principal reason given was subjective in 427 cases (61%); the remaining 273 patients (39%) reported that they had wanted earlier surgery, but were delayed by the waiting list for surgery (n = 211; 30.1%) or for MRI (n = 63; 9%). There was no dominant subjective reason: educational commitments accounted for 93 cases (13.3%), the end of a sporting career for 60 (8.6%), voluntary delay in seeking initial orthopaedic assessment (for example consulting a chiropractor first) 55 cases (7.9%), fear that surgery would fail 49 (7%), fear of surgery itself 36 (5.1%), occupational commitments 22 cases (3.1%), and pregnancy or childcare for 15 (2.1%) cases. The remaining 96 (13.7%) patients could not identify a specific reason for the delay.

Isolated ACL injury occurred in 530 (52%) cases; 246 (24.1%) patients had a combined injury involving the medial meniscus; 153 (15%) of the lateral meniscus; and 195 (19.1%) had more severe articular cartilage damage (grade 3 and 4 chondromalacia). Eighty-four patients had combined damage to the ACL, meniscus and articular cartilage.

Table 1 summarises associated injuries by group. In addition to ACL reconstruction, partial meniscectomy of the medial meniscus was performed in 64 (20%) patients in the early-operated group, and 182 (26%) patients in the delayed-operated group.

Lateral meniscal injury occurred in 46 (14.4%) patients in the early-operated group, and 107 (15.3%) in the delayed-operated group.

Table 2. Patients categorised by Tegner score

Tegner score	Preoperative	Postoperative
0	40	1
1	127	5
2	82	32
3	112	92
4	205	189
5	84	83
6	149	178
7	81	156
8	95	36
9	45	150
10	0	98
Average	4.40	6.17

Table 3. Difference between groups in mean activity score

	Tegner		Lysholm	
	Preoperative	Postoperative	Preoperative	Postoperative
Delayed surgery	4.44	5.50	73.86	91.60
Early surgery	4.61	6.20	72.00	93.12
Average	4.40	6.17	73.28	92.08

Cartilage damage was significantly less common in the early-operated group than in the delayed-operated group (12.2% vs 22.3%).

Overall, medial meniscal injury and severe articular cartilage damage were both significantly more common in the delayed-operated group ($p<0.05$). The difference between groups in lateral meniscal injury was not significant ($p>0.05$).

Tegner scores are shown in **Table 2:** the mean preoperative score was 4.49, rising to 5.72 postoperatively. The early-operated group had a higher mean postoperative score than the delayed-operated group (6.2 vs 5.5) (**Table 3**).

Postoperative Tegner score correlated significantly with the interval from injury to diagnosis ($\rho=-0.239$, $p<0.000$) and from injury to surgery ($\rho=-0.348$, $p<0.000$).

Postoperative Tegner score also correlated negatively and moderately strongly with the interval from surgery to the resumption of running ($r=-0.449$, $p<0.000$), and training ($r=-0.341$, $p<0.000$), and strongly with the interval to the resumption of competition ($r=-0.505$, $p<0.000$).

Preoperative Tegner score correlated significantly with preoperative Lysholm score ($r=0.138$, $p<0.000$). The mean preoperative Lysholm score was 73.28 (SD 18.17), rising significantly to 92.08 (SD 7.92) postoperatively. Early reconstruction was associated with a slightly higher, though not statistically significant, mean postoperative Lysholm score than delayed reconstruction (93.1 vs 91.6) (**Table 3**).

The Lysholm score also correlated negatively with the interval from surgery to resuming running ($r=-0.222$, $p<0.000$), training ($r=-0.098$, $p=0.01$), and competition ($r=-0.129$, $p<0.001$).

The interval from injury to surgery correlated moderately strongly with the interval from diagnosis to surgery ($\rho=0.355$, $p<0.000$).

Preoperative Tegner score showed a very weak positive correlation with the interval from diagnosis to surgery ($\rho=0.081$, $p=0.031$). Tegner score differed significantly by level of sporting activity ($\chi^2(30)=281.732$, $p<0.000$): professional athletes had significantly higher postoperative Tegner scores than recreational athletes or non-athletes.

Discussion

Active athletes represent the population at greatest risk of ACL injury; in this study, they were 30 times more likely to be represented than non-athletes [1–6,14]. The incidence of ACL injury is about 0.03 in the general population but as high as 1.6 among active athletes [6,14]. The epidemiological importance of this injury is further underlined by recent evidence that 1 in 4 young patients who return to high-risk sport after ACL reconstruction sustains a repeat rupture of the same or contralateral knee during their career [15,16].

Three questions dominate modern sports-traumatology debate on ACL surgery: should every complete rupture be operated on; what is the ideal time to operate; and when is it safe to return to training and competition after surgery.

Since natural processes such as graft ligamentisation cannot currently be accelerated, some authors recommend a return to unrestricted sporting activities at 6 months after reconstruction [9,10], while others argue that 9-12 months after reconstruction is more appropriate, given the risk of graft failure and re-rupture [4–6]. A safe return to competition at 6 months is possible only in the absence of knee instability, pain, swelling, or other complications, and only once proprioception and at least 90% of muscle strength have been restored [2,9,16]. Although the graft strength can initially exceed that of the native ligament, it weakens during ligamentisation (the process by which the graft is remodelled into a ligament) [16]. The graft does not begin to resemble a native ligament until around 6 months, with final maturation at approximately 1 year after the operation [17]. Vascularisation occurs 4 to 6 weeks after surgery, during which period the graft is structurally weaker and more vulnerable to tearing forces [17]. Remodelling of the new ligament is complete by 30 weeks, with maximum collagen strength, resistance, and proprioceptive recovery reached at around 39 weeks (9 months) [16–18]. Accordingly, there is growing evidence that returning to competition before 9 months substantially increases the risk of re-injury. Each additional month of delay reduces the risk by about 50% [19], and returning at 6 months carries up to 7 times the risk of returning at 9 months [17]. It

would therefore appear more effective to shorten the wait for surgery while allowing a longer interval before returning to sports [4–6,16–19].

Whether every ACL injury warrants surgery remains a topic of debate among surgeons and patients alike. Patients without significant post-injury symptoms, such as functional limitations and instability, are termed "copers" [19]; "non-copers", by contrast, cannot resume high-level sporting activity. With rehabilitation, however, copers may become non-copers and vice versa over time, further complicating decisions about whether and when to operate [19]. This is why assessing each patient's level of physical activity (via the Tegner score) is useful: sports can be stratified by risk into level 3 (lower risk), comprising cross-country skiing, cycling, swimming, and gym exercises; level 2, comprising volleyball, martial arts, gymnastics, ice hockey, tennis, squash, alpine/telemark skiing, snowboarding, dance/fitness and aerobics; and level 1 (highest risk), comprising handball, football and basketball (owing to the high risk movements such as pivoting, landing and rapid changes of direction these sports involve) [14,19]. In our sample, 96% of injuries occurred during sport, with two-thirds occurring during level 1 activities. Physical demands also vary within a single sport: for example, between a professional footballer training twice a day with frequent matches, an active recreational athlete training five times weekly, and an occasional recreational athlete training less than once a week. Notably, our sample included no ballerinas, dancers, or ice hockey players; this is not because ACL injuries do not occur in these groups, but because such activities are less popular in Serbia than ball sports [1–3,14,16].

Age, sex, and BMI are important considerations when planning the timing of surgery, particularly in adolescents, women, and obese patients who participate in high-risk activities such as skiing and ball sports [14,20–22]. We did not use hamstring grafts in this study; in general, our choice of graft is guided by the patient's occupation to avoid anterior knee pain in those whose work activities involve kneeling (for example: clergy, car mechanics, and plumbers, as well as female athletes) for whom we favour a hamstring graft. For professional and active recreational athletes, we favour a BPTB graft, consistent with recommendations that these are used for patients engaged in demanding physical activities such as football, basketball, handball, volleyball and alpine skiing [23–26]. In older patients, and in those engaged in lower-risk activity, hamstring reconstruction remains the method of choice [24,25]. Miller and Gladstone, and McAleese et al. found rerupture within 5 years of surgery to be 4.6 times more frequent with hamstring tendon (HT) reconstruction than with BPTB reconstruction among patients in the high-risk category (level 1) (19.7% vs 4.3%) [24,25]. Other authors report that revision rates after BPTB autografts remain within an acceptable range of 2-5% [2,26], which is why we used this graft in our sample of primary reconstructions.

The waiting time between injury and surgery depends on numerous patient-related factors (e.g. time to presentation, fear of surgery, motivation for treatment, preoperative knee status, and family or occupational commitments), as well as physician-related factors (e.g. interval to correct diagnosis, institutional waiting lists, and the surgeon's experience with this injury) [27]. In our experience, professional athletes typically request the earliest possible surgery, accepting that they will still lose at least 6 months of their career. In contrast, female athletes more often delay surgery towards the end of their careers, and students more often schedule surgery during academic holidays to minimise absence from study. A further complication is that one surgeon may agree to a professional athlete's request, whilst the other one may decline it, as they believe it may be less safe for the athlete in the long term. There is also a paramedical dilemma: if one surgeon does not grant a professional athlete's wish, another will, even if it is less safe in the long term.

There is evidence supporting the safety of surgery within the first week after the injury [28]. In comparison of patients with high recreational activity levels (Tegner score > 6) operated on within the first week versus those operated on between 6 and 10 weeks after injury, no significant difference was observed at 3 months and at 6 months. The early operated group had significantly less thigh muscle atrophy, although this difference subsequently resolved between groups. However, delayed surgery was associated with significantly higher costs, owing to longer rehabilitation and absence from work (89 vs 57 days), making early surgery more cost-effective [28].

In our sample, subjective factors accounted for 61% of delays. In contrast, other authors [4] report that fear of surgical failure (in 80% of cases) outweighs motivation and life factors such as occupation, family commitments and education. Our patients' mean wait for surgery, at almost 11 months, is comparable with that reported in Canadian public hospitals [7]. In contrast, waiting times in the United States and Scandinavia are typically 3-5 months after injury [5,8]. As our study included only patients treated in state institutions, it likely under-represents Serbian professional athletes, many of whom are treated privately and may receive even quicker diagnosis and treatment than those in our study sample. In our

delayed-operated group, it took about 8.5 months on diagnostics alone.

Some authors [20] believe that the timing of surgery is as important to the outcome as the surgical technique itself, in keeping with the principle that the smart choose the right moment, the superstitious anticipate it, and the less smart ignore it.

There is now substantial evidence that waiting for longer than 6 months for ACL surgery leads to recurrent knee instability and secondary injuries to other knee structures that may otherwise have been avoided [20,21,29–31]. We similarly found that medial meniscus injuries and severe articular cartilage damage were significantly more common in the delayed-operated group ($p<0.05$). A Norwegian study [32] estimated that each month's delay between injury and surgery increases the risk of articular cartilage injury by 1%, consistent with our findings that 12 months' delay was associated with an 11% higher rate of chondral pathology. On MRI, traumatic chondromalacia typically presents as localised, deep, focal cartilage defects with sharp, well-defined edges, often accompanied by acute bone marrow oedema or other joint injuries (such as meniscal tears) [32]. Degenerative chondromalacia, by contrast, features diffuse cartilage thinning, a broad, "crabmeat-like" zone of fibrillation, and chronic arthritic features such as subchondral cysts or bone spurs [32]; the older patients in our study with cartilage lesions showed features consistent with degenerative chondromalacia.

An Italian study following patients with combined ACL and meniscal injuries [31] likewise reported a mean interval of 11 months from injury to surgery. It concluded that older age and delayed surgery were associated with meniscal damage, while sex and BMI were not [22,31]. ACL rupture removes the knee's principal stabiliser, increasing load on other structures, such as the meniscus, owing to non-physiological redistribution of forces [22]. Nonetheless, excessive haste may not be warranted: a Swedish registry study that followed 18,425 patients found that reconstruction within the first 3 months after injury was associated with a significantly higher rate of revision surgeries (2.61% vs 1.64%), but with fewer meniscectomies and less post-traumatic osteoarthritis at 10 years [29].

Thirty-five years ago, the principal concern with early reconstruction (within 3 weeks of injury) was postoperative arthrofibrotic contracture [34]; this was reported in 18% of operations performed within 7 days of injury, compared with 6% in those performed more than a month after injury [35]. It was subsequently shown that even surgery within the first week, combined with more intensive rehabilitation, can avoid this complication [28]. Current opinion holds that the preoperative state of the knee (swelling, effusion, hyperthermia, muscle strength) is a more important determinant of outcome than the timing of surgery itself [27,30,36]. There is also evidence that preoperative quadriceps weakness (below 20% of physiological strength) is associated with significantly worse outcomes at 2 years [36].

Alongside developments in surgical technique, preoperative and postoperative rehabilitation protocols have been refined in recent decades [30], with an emphasis on achieving full range of motion, minimal or no swelling, a physiological walking/gait pattern, and adequate strength and muscle control before surgery. As this process takes time, patients opting for delayed surgery (beyond 6 months) should be advised that an unstable, unoperated knee can lead to further meniscal and cartilage damage, as well as significant pain and swelling [30]. We believe that an exception should be made for combined ACL injury with a locked (incarcerated) meniscus, where preoperative rehabilitation cannot achieve a satisfactory range of motion. Conversely, premature surgery may not allow time for spontaneous healing of the collateral ligaments, particularly the medial collateral ligament (MCL), which has a greater capacity for healing than the ACL or meniscus [33]. Most isolated and incomplete MCL tears are therefore managed conservatively, whereas ACL and meniscal tears are more often treated surgically [2,9,33]. Considerable debate remains, however, around combined ACL and complete (grade III) MCL injuries [33]; Westerman et al. found that MCL repair or reconstruction was associated with worse patient-reported outcomes and lower activity levels than non-operative MCL management at 2-year follow-up [33]. Most surgeons currently favour non-operative management of MCL with bracing for at least 6 weeks, followed by delayed ACL reconstruction [2,9,33].

A study of a similar-aged population, dominated by footballers, reached a conclusion comparable to ours: nearly one in 5 young athletes already had significant cartilage damage [37]. In that study, medial meniscal rupture was significantly more common among patients reconstructed more than 3 months after the injury, and chondral pathology was more pronounced among those operated on more than 6 months after rupture [37]. The same authors noted that some athletes continue to participate in sport despite injury, thereby worsening knee pathology while paradoxically reducing the apparent incidence of isolated ACL rupture. Other studies have similarly reported significantly more frequent meniscal injury and degenerative change with delays beyond 1 year, and identify 3 weeks to 3 months after injury as the optimal surgical window [32,37,38].

The success of ACL reconstruction in our sample is further evidenced by the mean Tegner score, which rose from 4.5 preoperatively to 5.7 postoperatively, an improvement most pronounced in the early-operated group (6.2). Across groups, mean Tegner score was lower among patients who waited longer for surgery. As expected, professional athletes achieved significantly higher Tegner scores than recreational athletes and non-athletes, reflecting the scale's design [2,6,9,39,40].

Tegner scores depend on both the type of sport played and whether it is pursued competitively or recreationally. Some studies have included only professional footballers (mean Tegner score 9) as subjects, yet found that only 65% of operated patients returned to the same sport, and only 55% regained their former level of activity [6]. Our results cannot reach an average score of 9, given that the sample is dominated by recreational athletes (66%) with a maximum score of 6-7. A study following amateur footballers' Tegner scores also found an association between scores and a history of knee injury, with a 0.8 point decrease per decade of age and scores 0.7 points lower in women than in men [39]. Other authors recorded a mean score of 8.7 2 years after ACL reconstruction, significantly higher than the preoperative value of 6.9 [40]. A study comparing autografts and allografts [41] found outcomes ranging from 6.8 to 7.2, suggesting that the Tegner score may be influenced by reconstruction method – a variable we controlled for by using a BPTB autograft throughout. We found no significant difference by age and sex between groups, although other studies report these as significant factors: one found a mean preoperative score of 5.58 in patients under 25 years versus 4.28 in older patients, and a postoperative score of 5.83 in the younger group versus only 4.33 in the older group [42]. Our findings are consistent with this body of evidence [39–42], with the Tegner score rising significantly after surgery, indicating functionality and sporting outcomes. A further indirect indicator of surgical success is shown in **Table 2**: 40 patients considered themselves disabled and unable to run before surgery, compared with only one after surgery. Similarly, no professional footballer competed at national or first division levels before surgery, compared with 98 afterwards. Overall, the longer the interval before diagnosis, surgery, and the resumption of running, training and competition, the lower the patients' resulting activity scores.

The Lysholm score remains one of the most widely used scales for pre- and postoperative assessment of knee function, despite dating from 1982 [13]. Scores of 91-100 are considered excellent, 84-90 good, 65-83 satisfactory, and below 64 poor. As surgical outcomes have improved, these criteria have tightened, such that only scores of 95-100 are now considered excellent [43]. In both of our groups, mean scores exceeded 90, indicating that operated patients had no significant residual problems with pain or instability (which together account for half the total score) or with daily activities.

Lysholm score also depends on the timing of the assessment as knee function continues to improve over time [44]. In one study, mean scores were 79.6 at 3 months after ACL reconstruction, 84.8 at 6 months, 88.0 at 1 year, and 89.0 at 2 years. Conversely, scores in another cohort fell from 82 to 76 between 2 years and a later follow-up, which was attributed to osteoarthritis [45]. Outcomes may also vary by sport: in one comparison, weightlifters had lower preoperative scores than non-weightlifters (58 vs 63) but higher postoperative scores (87 vs 84), reflecting greater improvement among those who undertake resistance training [46].

An earlier study comparing Lysholm scores between BPTB and HT groups found no significant difference in outcome (94 vs 93 points). However, BPTB results were more consistent, while the HT group had more complications, including infection and re-rupture [9]. Other studies report good outcomes even after revision surgery, with a mean score of 88 [2]. A comparison of early and delayed ACL reconstruction found that 1-year Lysholm scores were slightly higher after early surgery (87.0-93.3) than after delayed surgery (88.0-91.6) [28,47], a pattern broadly consistent with our own findings (93.1 vs 91.6), albeit with a small absolute difference. Other studies, like ours, have shown better outcomes when ACL reconstruction is performed within 3 to 5 months after injury than after a year [47]. Other authors, however, maintain that evidence for the superiority of early over delayed reconstructions remains insufficient [48].

This study has several limitations. We did not examine the effect of early support or rehabilitation on final surgical outcome, nor the relationship between activity scales and quality of life. A further limitation is the subjective nature of patient-reported outcomes, as we did not use instruments to measure anterior tibial translation or proprioception, nor did we formally test thigh muscle strength before clearing patients to return to sports. Future research might usefully compare more homogeneous groups of athletes - for example, early- versus late-operated professional footballers, or recreational basketball or handball players matched for competitive level.

Conclusion

The longer the interval before diagnosis, surgery, and the resumption of running, training and competition, the lower the resulting activity scores.

Patients' own (subjective) reasons are the most common cause of delayed surgery.

The ideal time for anterior cruciate ligament reconstruction is patient-specific and depends on the resolution of swelling and achievement of satisfactory preoperative range of motion and muscle strength.

Delaying surgery beyond 3 months after injury is associated with secondary injury to the medial meniscus and cartilage, and with poorer functional and sporting outcomes.

Early diagnosis and surgery should be a priority for health systems, as they support an earlier return to work and sporting activities, particularly among young patients.

References

1. Ristić V, Ristić S, Maljanović M, Milankov V, Harhaji V, Đuričin A. Quality of life after bilateral anterior cruciate ligament reconstructions. Med Pregl. 2015;68(9-10):308-15.
2. Milankov M, Miličić A, Savić D, Stanković M, Ninković S, Matijević R, et al. Revision anterior cruciate ligament reconstruction due to knee instability. Med Pregl. 2007;60(11-12):587-92.
3. Ristić V, Ristić S, Maljanović M, Đan V, Milankov V, Harhaji V. Risk factors for bilateral anterior cruciate ligament injuries. Med Pregl. 2015;68(5-6):192-7.
4. Hamdan M, Haddad BI, Amireh S, Abdel Rahman AMA, Almajali H, Mesmar H, et al. Reasons why patients do not return to sport post ACL reconstruction: a cross-sectional study. J Multidiscip Healthc. 2025;18:329-38.
5. Högberg J, Fridh E, Piussi R, Hamrin Senorski R, Cristiani R, Samuelsson K, et al. Delayed anterior cruciate ligament reconstruction is associated with lower odds of returning to preinjury physical activity level at 12 months follow-up. Arthroscopy. 2025;41(9):3401-12.e4.
6. Ardern CL, Taylor NF, Feller JA, Webster KE. Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. Br J Sports Med. 2014;48(21):1543-52.
7. Guenther ZD, Swami V, Dhillon SS, Jaremko JL. Meniscal injury after adolescent anterior cruciate ligament injury: how long are patients at risk? Clin Orthop Relat Res. 2014;472(3):990-7.
8. Dumont GD, Hogue GD, Padalecki JR, Okoro N, Wilson PL. Meniscal and chondral injuries associated with pediatric anterior cruciate ligament tears: relationship of treatment time and patient-specific factors. Am J Sports Med. 2012;40(9):2128-33.
9. Ristić V, Ninković S, Harhaji V, Stanković M, Savić D, Milankov M. Reconstruction of anterior cruciate ligament by using two different techniques. Med Pregl. 2010;63(11-12):845-50.
10. Shelbourne KD, Klotz CJ. What I have learned about the ACL: utilizing a progressive rehabilitation scheme to achieve total knee symmetry after anterior cruciate ligament reconstruction. Orthop Sci. 2006;11(3):318-25.
11. Upitnik o vašem zdravlju [Internet]. [cited 2026 Apr 15]. Available from: https://www.astas.rs/wp-content/uploads/2019/01/Upitnik-o-kvalitetu-zivota-posle-rekonstrukcije-prednjeg-ukrstenog-ligamenta-kolena.pdf.
12. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. Clin Orthop Relat Res. 1985;(198):43-9.
13. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med. 1982;10(3):150-4.
14. Ristić V, Ninković S, Harhaji V, Milankov M. Causes of anterior cruciate ligament injuries. Med Pregl. 2010;63(7-8):541-5.
15. Wiggins AJ, Grandhi RK, Schneider DK, Stanfield D, Webster KE, Myer GD. Risk of secondary injury in younger athletes after anterior cruciate ligament reconstruction: a systematic review and meta-analysis. Am J Sports Med. 2016;44(7):1861-76.
16. Ristić V, Ostojić F, Milović M, Milankov V. Knee proprioception of young volleyball players and ballerinas. Med Pregl. 2024;77(9-12):303-8.
17. Beischer S, Gustavsson L, Senorski EH, Karlsson J, Thomeé C, Samuelsson K, et al. Young athletes who return to sport before 9 months after anterior cruciate ligament reconstruction have a rate of new injury 7 times that of those who delay return. J Orthop Sports Phys Ther. 2020;50(2):83-90.
18. Dragičević-Cvjetković D, Erceg-Rukavina T, Nikolić S. Proprioception recovery after anterior cruciate ligament reconstruction – isokinetic versus dynamic exercises. Scr Med. 2021;52 (4):289-93.
19. Grindem H, Eitzen I, Engebretsen L, Snyder-Mackler L, Risberg MA. Nonsurgical or surgical treatment of ACL injuries: knee function, sports participation, and knee reinjury. The Delaware-Oslo ACL cohort study. J Bone Joint Surg Am. 2014;96(15): 1233-41.
20. Volpi P. Timing of anterior cruciate ligament reconstruction is just as important as a correct surgical procedure. Arthroscopy. 2021;37(4):1221-2.
21. Brambilla L, Pulici L, Carimati G, Quaglia A, Prospero E, Bait C, et al. Prevalence of associated lesions in anterior cruciate ligament reconstruction: correlation with surgical timing and with patient age, sex, and body mass index. Am J Sports Med. 2015;43(12):2966-73.
22. Ristić V, Šumar V, Rašović P, Milankov V. The impact of body mass index on results of reconstruction of anterior cruciate ligament. Med Pregl. 2021:74(11-12):354-61.
23. Milankov M, Obradović M, Vranješ M, Budinski Z. Bone-patellar tendon-bone graft preparation technique to increase cross-sectional area of the graft in anterior cruciate ligament reconstruction. Med Pregl. 2015;68(11-12):371-5.
24. Miller SL, Gladstone JN. Graft selection in anterior cruciate ligament reconstruction. Orthop Clin North Am. 2002;33 (4):675-83.
25. McAleese T, Welch N, King E, Roshan D, Keane N, Moran KA, et al. Primary anterior cruciate ligament reconstruction in level 1 athletes: factors associated with return to play, reinjury, and knee function at 5 years of follow-up. Am J Sports Med. 2025;53(4):777-90.
26. Shelbourne KD, Benner RW, Gray T. Return to sports and subsequent injury rates after revision anterior cruciate ligament reconstruction with patellar tendon autograft. Am J Sports Med. 2014;42(6):1395-400.
27. Evans S, Shaginaw J, Bartolozzi A. ACL reconstruction - it's all about timing. Int J Sports Phys Ther. 2014;9(2):268-73.
28. Eriksson K, von Essen C, Jönhagen S, Barenius B. No risk of arthrofibrosis after acute anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2018;26(10):2875-82.
29. Snaebjörnsson T, Hamrin Senorski E, Svantesson E, Westin O, Persson A, Karlsson J, et al. Graft fixation and timing of surgery are predictors of early anterior cruciate ligament revision: a cohort study from the Swedish and Norwegian knee liga-

ment registries based on 18,425 patients. JB JS Open Access. 2019;4(4): e0037.

30. Haro MS, Shelbourne DK. Prevention and management of loss of motion in anterior cruciate ligament surgery. Oper Techn Sports Med. 2016;24(1):45-54.

31. Turati M, Caliandro M, Pierpaoli E, Tassistro E, Galimberti S, Andreacchio A, et al. Age and time to surgery are associated with concomitant meniscal injuries in adolescent ACL tears: a retrospective cohort study were associated with a higher likelihood of meniscal damage. Healthcare (Basel). 2026;14(4):491.

32. Granan LP, Bahr R, Lie SA, Engebretsen L. Timing of anterior cruciate ligament reconstructive surgery and risk of cartilage lesions and meniscal tears: a cohort study based on the Norwegian National Knee Ligament Registry. Am J Sports Med. 2009;37(5):955-61.

33. Westermann RW, Spindler KP, Huston LJ, Wolf BR; MOON Knee Group. Outcomes of grade III medial collateral ligament injuries treated concurrently with anterior cruciate ligament reconstruction: a multicenter study. Arthroscopy. 2019;35(5):1466-72.

34. Shelbourne KD, Wilcken JH, Mollabashy A, DeCarlo M. Arthrofibrosis in acute anterior cruciate ligament reconstruction. The effect of timing of reconstruction and rehabilitation. Am J Sports Med. 1991;19(4):332-6.

35. Passler JM, Schippinger G, Schweighofer F, Fellinger M, Seibert FJ. Complications in 283 cruciate ligament replacement operations with free patellar tendon transplantation. Modification by surgical technique and surgery timing. Unfallchirurgie. 1995; 21(5):240-6.

36. Eitzen I, Holm I, Risberg MA. Preoperative quadriceps strength is a significant predictor of knee function two years after anterior cruciate ligament reconstruction. Br J Sports Med. 2009;43(5):371-6.

37. Razi M, Salehi S, Dadgostar H, Cherati AS, Moghaddam AB, Tabatabaiand SM, et al. Timing of anterior cruciate ligament reconstruction and incidence of meniscal and chondral injury within the knee. Int J Prev Med. 2013;4(Suppl 1):S98-103.

38. Church S, Keating JF. Reconstruction of anterior cruciate ligament: timing of surgery and the incidence of meniscal tear and degenerative change. J Bone Joint Surg Br. 2005;87(12):1639-42.

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39. Frobell RB, Svensson E, Gothrick M, Roos EM. Self-reported activity level and knee function in amateur football players: the influence of age, gender, history of knee injury and level of competition. Knee Surg Sports Traumatol Arthrosc. 2008;16(7):713-9.

40. Tegner Y, Lysholm J, Gillquist J, Oberg B. Two-year follow-up of conservative treatment of knee ligament injuries. Acta Orthop Scand. 1984;55(2):176-80.

41. Edgar CM, Zimmer S, Kakar S, Jones H, Schepsis AA. Prospective comparison of auto and allograft hamstring tendon constructs for ACL reconstruction. Clin Orthop Relat Res. 2008; 466(9):2238-46.

42. Kamien PM, Hydrick JM, Replogle WH, Go LT, Barrett GR. Age, graft size, and Tegner activity level as predictors of failure in anterior cruciate ligament reconstruction with hamstring autograft. Am J Sports Med. 2013;41(8):1808-12.

43. Panagopoulos A, Billis E, Floros GR, Stavropoulos T, Kaparounaki E, Moucho M, et al. Cross-cultural adaptation of the Greek versions of the Lysholm Knee Scoring Scale and Tegner Activity Scale. Cureus. 2020;12(7):e9372.

44. Risberg MA, Holm I, Steen H, Beynnon BD. Sensitivity to changes over time for the IKDC form, the Lysholm score, and the Cincinnati knee score: a prospective study of 120 ACL reconstructed patients with a 2-year follow-up. Knee Surg Sports Traumatol Arthrosc. 1999;7(3):152-9.

45. Jonsson H, Riklund-Ahlström K, Lind J. Positive pivot shift after ACL reconstruction predicts later osteoarthrosis 63 patients followed 5–9 years after surgery. Acta Orthop Scand. 2009;75(5):594-9.

46. Tyler TF, McHugh MP, Gleim GW, Nicholas SJ. The effect of immediate weightbearing after anterior cruciate ligament reconstruction. Clin Orthop Relat Res. 1998;(357):141-8.

47. Ahlen M, Lidén M. A comparison of the clinical outcome after anterior cruciate ligament reconstruction using a hamstring tendon autograft with special emphasis on the timing of the reconstruction. Knee Surg Sports Traumatol Arthrosc. 2011;19(3):488-94.

48. Shen X, Liu T, Xu S, Chen B, Tang X, Xiao J, et al. Optimal timing of anterior cruciate ligament reconstruction in patients with anterior cruciate ligament tear: a systematic review and meta-analysis. JAMA Netw Open. 2022;5(11):e2242742.

BASAL CELL CARCINOMA OF THE SKIN – A FOUR-YEAR EXPERIENCE OF THE UNIVERSITY CLINICAL CENTER OF VOJVODINA

BAZOCELULARNI KARCINOM KOŽE – ČETVOROGODIŠNjE ISKUSTVO UNIVERZITETSKOG KLINIČKOG CENTRA VOJVODINE

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Abstract

Introduction. Basal cell carcinoma is the most common non-melanoma skin cancer. It predominantly occurs in sun-exposed areas, in individuals older than 50 years, and more frequently in men. The most important risk factors are skin phototype and ultraviolet radiation exposure. Most lesions are located on the face, scalp, and neck. Surgical treatment remains the most effective approach as it enables complete tumour excision with clear margins and subsequent histopathological analysis. The study aimed to analyse the incidence, type, and distribution of basal cell carcinoma of the skin, as well as the association between risk factors, age, and sex, in patients treated at the Clinic for Plastic and Reconstructive Surgery, University Clinical Center of Vojvodina, between 2020 and 2023. **Material and Methods.** A retrospective study was conducted using data obtained from hospital medical records and the institutional information system. **Results.** A total of 802 patients were included; the mean age was 73.3 years. Lesions were most frequently located on the face (25.3%). The most common histopathological subtype was the mixed type, comprising nodular and infiltrative components (47.1%). The largest proportion of patients sought medical attention between one month and one year after first noticing the lesion (32.9%). A previous history of the disease was more common in men than in women. **Conclusion.** Basal cell carcinoma is often under-represented in cancer registries because of its relatively low mortality. Monitoring epidemiological trends is essential for prevention, early detection, and effective disease control.

Key words: Basal Cell Carcinoma; Skin Neoplasms; Epidemiology; Histology; Biopsy; Risk Factors

Sažetak

Uvod. Bazocelularni karcinom je najčešći nemelanomski maligni tumor kože. Najčešće se javlja na područjima izloženim suncu, kod osoba starijih od 50 godina i kod muškaraca. Najvažniji faktori rizika su fototip kože i ultraljubičasto zračenje. Većina lezija lokalizovana je na licu, glavi i vratu. Hirurško lečenje predstavlja najefikasniji terapijski pristup jer omogućava potpuno uklanjanje tumora sa rubom zdravog tkiva i patohistološku analizu. Cilj rada bio je da se analiziraju učestalost, tip i distribucija bazocelularnog karcinoma kože, kao i povezanost faktora rizika, starosti i pola kod pacijenata lečenih na Klinici za plastičnu i rekonstruktivnu hirurgiju Univerzitetskog kliničkog centra Vojvodine u periodu od 2020. do 2023. godine. **Materijal i metode.** Retrospektivna studija sprovedena je analizom podataka iz medicinske dokumentacije i informacionog sistema ustanove. **Rezultati.** U studiju su uključena 802 pacijenta, prosečne starosti 73,3 godine. Promene su najčešće bile lokalizovane na licu (25,3%). Najzastupljeniji histološki tip bio je mešoviti, koji je obuhvatao kombinaciju nodularnog i infiltrativnog tipa (47,1%). Najveći broj pacijenata javio se lekaru u periodu od jednog meseca do jedne godine nakon uočavanja promene (32,9%). Prethodna pojava bolesti bila je češća kod muškaraca. **Zaključak.** Bazocelularni karcinom se često ne evidentira u registrima karcinoma zbog niskog mortaliteta. Praćenje epidemioloških trendova važno je za prevenciju, rano otkrivanje i adekvatnu kontrolu bolesti.

Ključne reči: bazocelularni karcinom; tumori kože; epidemiologija; histologija; biopsija; faktori rizika

Introduction

Basal cell carcinoma is a slow-growing malignant tumour and the most common non-melanoma skin cancer, predominantly occurring on sun-exposed areas in fair-skinned individuals [1]. It originates from immature pluripotent cells of the basal layer of the epidermis, the outer root sheath of hair follicles, sebaceous glands, and other cutaneous adnexal structures. Basal cell carcinoma is characterized by locally infiltrative and occasionally destructive growth [1]. Metastases are exceedingly rare, with an estimated incidence ranging from 0.0028% to 0.5% [2]. The disease occurs more frequently in individuals older than 50 years and is approximately twice as common in men as in women [3]. The highest incidence rates have been

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reported in Australia, where recent population-based estimates indicate approximately 770 new cases per 100,000 persons annually [4].

The most important aetiological factors include skin phototype - particularly Fitzpatrick skin types I and II - and environmental exposure, primarily to natural and artificial ultraviolet radiation, including tanning beds. Other factors implicated in skin carcinogenesis include X-ray exposure, alpha- and beta-radiation, chemical carcinogens such as tar, resins, soot, arsenic, asbestos, immunosuppressive therapy, a family history of skin cancer, and specific genodermatoses associated with oncogenic transformation, including Gorlin–Goltz syndrome, xeroderma pigmentosum, and albinism [5].

Cumulative exposure to solar ultraviolet radiation is considered the principal environmental risk factor for the development of basal cell carcinoma. Prolonged outdoor exposure, particularly among those who work outdoors, such as farmers, construction workers, and sailors, has been implicated in its development [6]. Furthermore, recreational sun exposure during childhood and adolescence significantly increases the risk of developing basal cell carcinoma later in life, suggesting that these periods may be critical in determining the risk of the disease in adulthood [7].

Ultraviolet radiation induces structural damage to epidermal deoxyribonucleic acid (DNA). Whilst such damage is normally repaired, inadequate cellular repair mechanisms may permit the persistence and replication of induced mutations, ultimately leading to malignant transformation of affected tissues. In addition to its mutagenic effects, ultraviolet radiation exerts local immunosuppressive activity by reducing the number of Langerhans cells and stimulating epidermal suppressor T lymphocytes [8].

The majority of basal cell carcinoma lesions occur on sun-exposed areas of the skin, particularly the face, scalp, and neck, accounting for approximately 90% of all such neoplasms. They are especially common on the head and neck above an imaginary line connecting the corner of the mouth and the earlobe [9]. The most common clinical presentation of early basal cell carcinoma is a light pink papule with a smooth, shiny surface and prominent telangiectasia. As the lesion progresses, central crusting or ulceration may develop. Patients frequently present with an enlarging, non-healing lesion that may occasionally bleed and may also be associated with pruritus. Tumour spread typically follows the path of least resistance, including along the periosteum, perichondrium, perineurium, and fascial planes. Recurrences have been shown to occur more frequently in patients who delayed surgical treatment for a prolonged period [10].

Several clinical variants of basal cell carcinoma have been described, including nodular, ulcerative, superficial, pigmented, morpheaform, and cystic forms [11]. The prognosis of basal cell carcinoma is closely related to tumour size. Giant basal cell carcinoma, defined as a lesion exceeding 5 cm in diameter, is generally associated with the poorest prognosis [8].

In 2006, the World Health Organisation published a classification of skin tumours recognising eight histopathological subtypes of basal cell carcinoma: superficial, nodular, micronodular, infiltrative, fibroepithelial, basosquamous, keratotic, and basal cell carcinoma with adnexal differentiation [12]. From a surgical perspective, the distinction between aggressive and non-aggressive subtypes is particularly important. Aggressive variants include infiltrative, morpheaform, micronodular, basosquamous, and mixed infiltrative–morpheaform or nodular–infiltrative forms, whereas superficial, pigmented, and nodular subtypes are considered non-aggressive [13]. Aggressive subtypes characteristically grow as continuous strands of tumour cells along paths of least resistance, including nerves and fascial structures, and represent the most common cause of recurrence [1].

Treatment options may be either non-surgical or surgical. Non-surgical approaches include imiquimod, photodynamic therapy, and radiotherapy. Surgical excision remains the treatment of choice, as it enables complete removal of the lesion with an adequate margin of healthy tissue, and the excised specimen is subsequently submitted for histopathological examination, which provides definitive confirmation of the diagnosis [13].

This study aimed to analyse the demographic, clinical, and histopathological characteristics of patients with basal cell carcinoma and to evaluate associations between age, sex, smoking status and tumour-related variables.

Material and Methods

This study was conducted as a retrospective analysis. Patients with histopathologically confirmed basal cell carcinoma who were treated at the Clinic for Plastic and Reconstructive Surgery, University Clinical Center of Vojvodina, between 1 January 2020 and 31 December 2023, were included. The unit of analysis was the individual patient; in patients with more than one lesion, data were recorded at the patient level rather than separately for each lesion. The database was accessed after the end of the study period.

Table 1. Distribution of Lesion Locations

Location	N	%	Male	%	Female	%
Face	203	25.3	86	21.1	117	29.6
Back	184	22.9	94	23.1	90	22.8
Scalp	166	20.7	99	24.3	67	17
Upper extremity	83	10.3	47	11.5	36	9.1
Trunk	83	10.3	45	11.1	37	9.4
Lower extremity	43	5.4	16	3.9	27	6.8
Neck	40	5.0	20	4.6	20	5.1
Genital region	1	0.1	0	0	1	0.1

Disease-related data were collected from hospital medical records via the Clinical Information System. Patients were identified using diagnosis-specific search criteria. A total of 27 referral diagnosis codes according to the International Classification of Diseases, Tenth Revision, were recorded among patients who were subsequently confirmed to have histopathologically verified basal cell carcinoma. The diagnostic codes considered for inclusion were D48.5 and C44.0–C44.9.

The following variables were collected for all participants: sex, age, time interval between the appearance of the lesion and the first medical consultation, tumour location, histopathological subtype, and previous history of basal cell carcinoma. In this study, a previous history of basal cell carcinoma was defined as any earlier occurrence of the disease - that is, one or more histopathologically confirmed basal cell carcinomas diagnosed before the current presentation, irrespective of anatomical site - rather than local recurrence of a previously treated tumour at the same site. Local recurrence could not be reliably distinguished from new primary tumours arising in previously treated patients; accordingly, all patients with any prior history of basal cell carcinoma, including suspected local recurrences, were classified as having a previous history of the disease. Patients whose current tumour was their first diagnosed basal cell carcinoma were classified as having primary disease. Given the considerable variability in lesion locations, sites were categorised into eight anatomical groups. Lesions on the shoulders were included in the upper extremity group, whilst trunk lesions were divided into the anterior trunk (chest and abdomen) and posterior trunk (back).

Statistical analysis was performed using IBM SPSS Statistics software. Categorical variables were presented as frequencies (N) and percentages (%). The chi-square test was used for categorical variables and Student's t-test for continuous variables. Statistical significance was set at $p<0.05$.

The study was approved by the Ethics Committee of the University Clinical Center of Vojvodina (approval number 00-251).

Results

A total of 802 patients were included in the study, comprising 407 men and 395 women. The mean age was 73.30 years (SD = 11.72; range 32-104 years). No statistically significant difference was observed in the sex distribution of patients ($p = 0.67$). However, men were significantly older than women (mean age 74.34 ± 11.02 vs 72.20 ± 12.31 years, respectively; $p < 0.01$).

Patients with a history of skin lesions at the time-of presentation of the current presentation were significantly older than those without (75.32 ± 9.81 vs. 72.49 ± 12.32 years, respectively; $p < 0.01$). A significant difference was also observed concerning smoking status, with non-smokers being older than smokers ($p = 0.02$), with a mean age difference of 3.15 years.

The majority of participants were residents of Novi Sad, accounting for 426 patients (53.1%).

The distribution of lesion locations is presented in **Table 1**. A statistically significant association was found between lesion location and sex ($p < 0.05$). Scalp lesions were significantly more common in men than in women (99 vs 67 cases), whereas facial lesions were more frequently observed in women than in men (117 vs 86 cases).

The most common histopathological finding was *Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi* (N = 378; 47.1%), followed by *Carcinoma basocellulare infiltrativum cutis et texti fibrosi* (N = 111; 13.8%). The distribution of histopathological diagnoses is presented in **Table 2**.

Significant sex-related differences were observed in the distribution of certain histopathological findings ($p < 0.01$). Specifically, *Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi* was more frequently diagnosed in women, whereas *Carcinoma basocellulare infiltrativum cutis*, *Carcinoma basocellulare cutis typus superficialis*, and *Carcinoma*

Table 2. Distribution of Histopathological Diagnoses

Histopathological Diagnosis	N	%	Male	%	Female	%
Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi	378	47.1	172	42.2	206	52.2
Carcinoma basocellulare infiltrativum cutis	91	11.3	57	14	34	8.6
Carcinoma basocellulare exulceratum et infiltrativum cutis	86	10.7	43	10.6	43	10.9
Carcinoma basocellulare cutis typus superfitialis	29	3.6	21	5.2	8	2.0
Carcinoma basocellulare exulceratum et infiltrativum cutis typus superfitialis	9	1.1	2	.5	7	1.8
Carcinoma basocellulare cutis	7	0.9	4	1	3	0.8
Carcinoma basocellulare infiltrativum cutis typus superfitialis	13	1.6	4	1	9	2.3
Carcinoma basocellulare infiltrativum cutis et texti fibrosi	111	13.8	68	16.7	43	10.9
Carcinoma basocellulare exulceratum cutis	8	1	5	1.2	3	0.8
Carcinoma basocellulare exulceratum cutis typus superfitialis	9	1.1	5	1.2	4	1
Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et adiposi subcutanei	36	4.5	13	3.2	23	5.8
Carcinoma basocellulare infiltrativum cutis et texti fibrosi et adiposi subcutanei	2	0.2	0	0	2	0.5
Carcinoma basocellulare infiltrativum cutis et texti fibrosi et adiposi subcutanei et texti muscularis	4	0.5	3	0.7	1	0.3
Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et texti adiposi et musculi striatii	6	0.7	3	0.7	3	0.8
Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et texti adiposi et musculi striatii et spatii perineuralis	1	0.1	1	0.2	0	0
Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et musculi arrector pili	3	0.4	3	0.7	0	0
Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et chondroides et adiposi subcutanei	2	0.2	2	0.5	0	0
Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et muscularis et spatii perineuralis	2	0.2	1	0.2	1	0.3
Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et texti adiposi subcutanei et spatii perineuralis	6	0.7	1	0.2	5	1.3

basocellulare infiltrativum cutis et texti fibrosi were more common in men. No statistically significant sex-related differences were identified for the remaining histopathological diagnoses.

Among scalp lesions, the most common histopathological findings were *Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi* (N = 77; 46.4%), *Carcinoma basocellulare infiltrativum cutis et texti fibrosi* (N = 24; 14.5%), and *Carcinoma basocellulare infiltrativum cutis* (N = 23; 13.9%). Similarly, among facial lesions, the most frequent diagnosis was *Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi* (N = 102; 50.2%), followed by *Carcinoma basocellulare infiltrativum cutis* (N = 26; 12.8%) and *Carcinoma basocellulare infiltrativum cutis et texti fibrosi* (N = 20; 9.9%).

No statistically significant association was found between histopathological subtype and lesion location (p = 0.86), nor between histopathological subtype and previous history of basal cell carcinoma (p = 0.81). Regarding the time interval before presentation, patients diagnosed with *Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi* most frequently sought medical attention between one and five years after first noticing the lesion. No significant differences in the distribution of histopathological findings were observed according to smoking status (p = 0.69).

Patients differed with regard to the time interval between first noticing the lesion and seeking medical attention; the distribution of these intervals is presented in **Figure 1**. Within the study cohort, 572 patients (71.2%) presented with a primary lesion, whereas 231 patients (28.8%) reported a previous history of basal cell carcinoma.

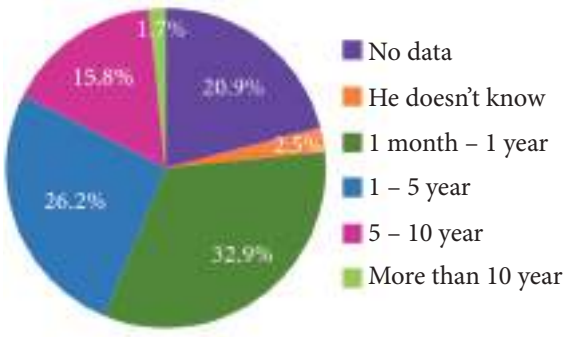

Figure 1. Time Interval Between Initial Detection of the Lesion and First Medical Consultation

Among male patients, data on time to presentation were unavailable for 72 individuals, and 7 patients were unable to specify the duration. A total of 140 men sought medical attention between 1 month and 1 year after noticing the lesion, 115 between 1 and 5 years, 65 between 5 and 10 years, and 8 after more than 10 years. Among female patients, data were unavailable for 96 individuals, and 13 were unable to recall the duration. A total of 124 women presented between 1 month and 1 year after lesion onset, 95 between 1 and 5 years, 61 between 5 and 10 years, and 6 after more than 10 years. Overall, information on the time interval between lesion onset and the first medical consultation could not be retrieved for 168 patients (20.9%), and a further 20 patients (2.5%) were unable to specify it; this variable was therefore available for analysis in 614 patients (76.6%).

No statistically significant association was found between sex and time to presentation ($p = 0.13$).

A statistically significant relationship was observed between lesion location and time to presentation ($p < 0.01$). Scalp lesions were more common among patients who sought medical attention between 1 and 5 years after first noticing the lesion, and less common among those presenting between 5 and 10 years. Trunk lesions were disproportionately less frequent among patients presenting between 1 and 5 years after lesion onset. Patients presenting between 5 and 10 years after first noticing the lesion more frequently had lesions located on the back. Facial lesions, by contrast, were more common among patients who sought medical attention relatively early - within 1 month to 1 year after lesion onset - and, as expected, less frequent among those presenting between 5 and 10 years.

A previous history of basal cell carcinoma was significantly more common in men ($N = 141$) than in women ($N = 90$) ($p < 0.01$; odds ratio for male sex 1.80, 95% CI 1.32–2.45). Among male patients, 266 had no previous history of the disease, compared with 305 female patients.

Borderline differences were observed in the distribution of previous disease according to lesion location ($p = 0.06$). Scalp and face lesions appeared somewhat more common among patients with a previous history of basal cell carcinoma, whereas back lesions were more frequently observed among those presenting for the first time.

Within the study population, 719 patients (89.5%) were non-smokers, and 84 (10.5%) were smokers. Significant differences in lesion location were observed according to smoking status ($p = 0.011$). Facial lesions were disproportionately more common among smokers, whilst back lesions were more frequently observed among non-smokers. No statistically significant association was found between smoking status and the time to presentation.

Discussion

Basal cell carcinoma is a slow-growing malignant tumour arising from the basal layer of the epidermis, the outer root sheath of hair follicles, or sebaceous glands. It is the most common skin malignancy, accounting for up to 80% of all diagnosed skin cancers, and its incidence continues to increase worldwide [14].

Rising incidence rates of basal cell carcinoma have been reported globally for several decades. In Europe, the incidence is estimated to increase by approximately 5.5% per year [15]. The highest rates worldwide have been reported in Australia and New Zealand. A study conducted across 38 countries between 1955 and 2007 identified Australia as having the highest incidence, exceeding 1000 new cases per 100,000 population annually [16]. As basal cell carcinoma predominantly affects fair-skinned individuals, disease incidence varies according to the racial and ethnic composition of a given population [17]. Regrettably, no dedicated registry providing current epidemiological data on basal cell carcinoma in the Republic of Serbia could be identified. According to national cancer statistics, 1,830 and 1,715 new cases of non-melanoma skin cancer were diagnosed among men and women, respectively, in Serbia in 2018 [18].

Although basal cell carcinoma may occur earlier in life, either sporadically or in association with certain genodermatoses, increasing age is an independent risk factor [3]. The incidence approximately doubles between the ages of 40 and 70 years [8]. In our study, the mean age was 73.30 ± 11.72 years, consistent with previous epidemiological reports [3]. For example, German cancer statistics from 2014 reported a mean age of 72 years in patients with basal cell carcinoma, with men accounting for 52% of cases [19]. In contrast to studies reporting a male predominance with a male-to-female ratio ranging from 1.5:1 to 2:1, no statistically significant sex-related difference in disease occurrence was observed in our cohort [20].

Although mortality is low owing to the rarity of metastasis, basal cell carcinoma is associated with considerable morbidity and represents a substantial burden on healthcare systems worldwide. The most common anatomical sites are the head and neck, accounting for 70–98.4% of cases, followed by the upper extremities and back [21]. In our study, lesions were most frequently located on the face, followed by the back and scalp. Of particular note was the identification of a single case of genital basal cell carcinoma in a female patient, an exceptionally rare localisation.

As an example, Popadić et al. reported a case of genital basal cell carcinoma in a 55-year-old man, emphasising the rarity of this presentation [22].

A statistically significant sex-related difference was observed in lesion location. Scalp lesions were more common among men, whilst facial lesions were more frequently reported among women. These findings are consistent with those reported by Souza et al., who demonstrated a tendency for women to develop lesions on the central face - particularly the nose and upper lip - whilst men more commonly presented with lesions on the scalp, lateral facial regions, ears, and hair-bearing scalp [23]. These differences may be explained primarily by behavioural and anatomical factors, including longer hairstyles in women and a lower prevalence of severe androgenetic alopecia compared with men. Although several studies have reported a predilection for trunk lesions in men and lower-extremity lesions in women, no significant sex-related differences were observed at these anatomical sites in our study [24].

Numerous histopathological classifications of basal cell carcinoma have been proposed. The need for a simplified and clinically relevant classification led Sexton et al. to define six major histopathological subtypes: nodular (including ulcerated forms), superficial, micronodular, infiltrative, sclerosing, and mixed [25]. According to most authors, the nodular subtype is considered a low-risk, whilst the infiltrative subtype is classified as high risk [26]. Superficial basal cell carcinomas account for approximately 10% of all cases and are typically located on the trunk or extremities; although generally regarded as a low-risk, they demonstrate a tendency toward recurrence owing to their multifocal growth pattern [13].

To facilitate the interpretation of our results, lesions exhibiting both ulcerative and infiltrative features were classified as a mixed subtype. The most common histopathological finding in our study was mixed basal cell carcinoma involving the skin and subcutaneous tissue (*Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi*), accounting for 47.1% of cases, followed by infiltrative basal cell carcinoma involving the skin and subcutaneous tissue (*Carcinoma basocellulare infiltrativum cutis et texti fibrosi*), which accounted for 13.8%. When all infiltrative variants were combined, irrespective of tissue depth or extent of involvement, the overall frequency of infiltrative basal cell carcinoma was 27.4%. The superficial subtype was identified in only 3.6% of cases, whilst the ulcerative subtype alone accounted for 2.1% of cases.

These findings differ from those reported in most previous studies [24], in which the nodular subtype has consistently been the most common histopathological variant. For example, Roš et al. found that the nodular subtype represented 57% of all basal cell carcinomas examined [14]. One possible explanation is that our institution is a tertiary referral centre.

Significant sex-related differences in the distribution of histopathological subtypes were observed ($p < 0.01$). The mixed subtype was more frequently diagnosed in women, whilst infiltrative and superficial subtypes were more common in men. These findings are partially consistent with those reported by Pyne et al., who demonstrated a higher prevalence of both superficial and aggressive subtypes, including infiltrative basal cell carcinoma, in male patients [27]. However, Scrivener et al. reported somewhat different results, noting a higher proportion of nodular basal cell carcinomas in men than in women (79.9% vs 77.5%), whilst infiltrative subtypes were more frequent among women (7.2% vs 5.2%) [24].

Regarding scalp and facial lesions, the most common histopathological findings in our study were the mixed subtype (46.4% and 50.2%, respectively) and the infiltrative subtype (28.4% and 22.7%, respectively), consistent with previous studies reporting that infiltrative basal cell carcinoma most frequently occurs in the head and neck region [12]. No statistically significant association was observed between histopathological subtype and lesion location ($p = 0.86$), nor between histopathological subtype and previous history of basal cell carcinoma ($p = 0.81$). Regarding time to presentation, patients with the mixed subtype most commonly presented between one and five years after first noticing the lesion.

Patients differed in the interval between lesion onset and the first medical consultation. Within our study population, 572 patients (71.2%) presented with a first diagnosed basal cell carcinoma, whilst 231 patients (28.8%) had a previous history of the disease. The largest proportion of patients (32.9%) sought medical attention between one month and one year after first noticing the lesion, whilst 26.2% presented between one and five years. It has been reported that 30–50% of patients diagnosed with primary non-melanoma skin cancer will develop another within five years, representing a nearly tenfold increased risk of developing a subsequent basal cell carcinoma or cutaneous squamous cell carcinoma compared with the general population [28]. These findings highlight the importance of patient education and regular dermatological and dermoscopic follow-up.

Basal cell carcinomas are commonly classified as low-risk or high-risk tumours with respect to recurrence [7]. High-risk tumours include lesions larger than 2 cm in diameter, tumours located in the central

facial region (particularly around the eyes, nose, and lips), clinically ill-defined lesions, aggressive histopathological subtypes, and recurrent tumours [7,29]. Surgical margins are generally determined according to tumour size: lesions up to 10 mm are typically excised with 3–5 mm margins of clinically healthy tissue, whilst tumours measuring 10–20 mm usually require margins of at least 5 mm [29]. The primary goal of treatment is complete tumour excision with an adequate safety margin, followed by reconstruction of the resulting defect whilst preserving function and achieving the best possible aesthetic outcome [30].

In our study, a previous history of basal cell carcinoma was more common in men (N = 141) than in women (N = 90). Borderline differences were observed between previous disease history and lesion location (p = 0.06). Scalp and facial lesions appeared somewhat more frequent among patients with a previous history of the disease, whilst back lesions were more common in those presenting with a primary tumour. These findings are consistent with those of Bøgelund et al. [31], who reported that trunk lesions carried the most favorable prognosis, whilst tumours on the head carried the highest risk of recurrence. The authors also demonstrated that recurrence risk depends on tumour size, anatomical location, treatment modality, and the clinical experience of the treating surgeon. Notably, previous studies have shown that the risk of developing a new basal cell carcinoma decreases over time, from 11.6% in the first year after treatment to 6.3% in the second year [32].

Previous studies have demonstrated that basal cell carcinoma and cutaneous squamous cell carcinoma exhibit markedly different associations with cigarette smoking [33]. Specifically, Dusingize et al. reported that current smoking was associated with a reduced risk of basal cell carcinoma but an increased risk of cutaneous squamous cell carcinoma [33]. In our study, non-smokers accounted for the majority of participants (89.5%), whilst smokers represented 10.5% of the cohort. Facial lesions were disproportionately more common among smokers, whilst back lesions were more frequently observed among non-smokers (p = 0.011). No comparable studies examining differences in the anatomical distribution of basal cell carcinoma between smokers and non-smokers could be identified, limiting direct comparison with previously published data.

Several limitations of this study should be acknowledged. First, the study relied on medical records held in the Clinical Information System, which were not uniformly documented. Second, variables such as the time to presentation and smoking status were obtained from patient medical histories and thus dependent on self-reporting, which could not be independently verified. These factors may have introduced information bias. Finally, this was a single-centre retrospective study conducted at a tertiary referral centre. As such, centres tend to manage more complex and advanced cases, which may have contributed to an over-representation of aggressive histopathological subtypes relative to the general population, and limit the generalisability of the findings to other clinical settings.

Conclusion

Basal cell carcinoma predominantly affects older individuals and remains an important public health challenge owing to its high incidence and potential for local tissue destruction. The predominance of mixed and infiltrative histopathological subtypes in our cohort, in contrast to findings reported in most epidemiological studies, may reflect specific characteristics of the treated population at a tertiary referral centre. Male patients more frequently had a previous history of the disease, and significant sex-related differences were observed in lesion localisation. The observed delays in seeking medical attention further emphasise the importance of patient education, regular skin examinations, and early treatment. Ongoing surveillance of epidemiological and clinicopathological patterns may facilitate earlier diagnosis, improve treatment outcomes, and reduce disease recurrence.

References

1. Lang PG, Maize J. Basal cell carcinoma. In: Rigel DS, Friedman R, Dzubow LM, Bystryn JC, Reintgen DS, Marks R. Cancer of the skin. Philadelphia: Elsevier Saunders; 2005. p. 101-25.

2. Walling HW, Fosko SW, Geraminejad PA, Whitaker DC, Arpey CJ. Aggressive basal cell carcinoma: presentation, pathogenesis, and management. Cancer Metastasis Rev. 2004;23(3-4):389-402.

3. Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Aust. 2006;184(1):6-10.

4. Olsen CM, Pandeya N, Green AC, Ragaini BS, Venn AJ, Whiteman DC. Keratinocyte cancer incidence in Australia: a review of population-based incidence trends and estimates of lifetime risk. Public Health Res Pract. 2022;32(1):3212203.

5. Dimitrijević MV. Epitelni maligni tumori kože. In: Dimitrijević M, editor. Maksilofacijalna hirurgija. Beograd: Medicinski fakultet Univerziteta u Beogradu; 2020. p. 165-70.

6. Cameron MC, Lee E, Hibler BP, Barker CA, Mori S, Cordova M, et al. Basal cell carcinoma: epidemiology, pathophysiology, clinical and histological subtypes, and disease associations. J Am Acad Dermatol. 2019;80(2):303-17.

7. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med. 2005;353(21):2262-9.

8. Crowson AN. Basal cell carcinoma: biology, morphology and clinical implications. Mod Pathol. 2006;19 Suppl 2:S127-47.

9. Migden MR, Chen L, Silapunt S, editors. Basal cell carcinoma: advances in treatment and research. 1st ed. Cham: Springer; 2020. p. 290.

10. Leibovitch I, Huilgol SC, Selva D, Richards S, Paver R. Basal cell carcinoma treated with Mohs surgery in Australia I. Experience over 10 years. J Am Acad Dermatol. 2005;53(3):445-51.

11. Reifenberger J, Ruzicka T. Basal cell carcinoma. In: Braun-Falco O, Burgdorf WHC, Plewig G, Wolff HH, Landthaler M, editors. Braun-Falco's dermatology. Heidelberg: Springer Medizin Verlag; 2009. p. 1348-56.

12. LeBoit PE, Burg G, Weedon D, Sarasin A. World Health Organisation classification of tumors. Pathology and genetics of skin tumours. Lyon: IARC Press. 2006. p. 10-33.

13. Dimitrijević M, Brašanac D, Todorović N, Petrović M, Dimitrijević AM. Basal cell carcinoma–principles of treatment. Srp Arh Celok Lek. 2023;151(1-2):98-105.

14. Roš T, Gajić B, Rajić N, Ivkov-Simić M, Gajinov Z. Basal cell carcinoma: a frequent challenge/bazocelularni karcinom: čest izazov. Serbian Journal of Dermatology and Venereology. 2013;4(1):5-30.

15. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012;166(5):1069-80.

16. Vukić L. Etiopatogeneza, klinička slika, dijagnostika i liječenje bazocelularnog karcinoma [master thesis]. Rijeka: Sveučilište u Rijeci, Medicinski fakultet; 2023.

17. Gangan R. Basal cell carcinoma: epidemiology. J Skin Sex Transm Dis. 2022;4(2):157-63.

18. Institute of Public Health of Serbia "Dr Milan Jovanović Batut", Department for Prevention and Control of Noncommunicable Diseases. Malignant tumours in Republic of Serbia 2018. Serbian cancer registry. Beograd: Institute of Public Health of Serbia "Dr Milan Jovanović Batut"; 2020.

19. Robert Koch-Institut. Krebs in Deutschland für 2013/2014. 11. Ausgabe. Berlin: Robert Koch-Institut; 2017.

20. Andersen LK, Davis MD. Sex differences in the incidence of skin and skin-related diseases in Olmsted County, Minnesota, United States, and a comparison with other rates published worldwide. Int J Dermatol. 2016;55(9):939-55.

21. Griffiths RW, Suvarna SK, Stone J. Basal cell carcinoma histological clearance margins: an analysis of 1539 conventionally excised tumours. Wider still and deeper? J Plast Reconstr Aesthet Surg. 2007;60(1):41-7.

22. Popadić S, Tanasilović S, Živanović D, Medenica L. Genital superficial basall cell carcinoma - a case report/Bazocelularni karcinom kože u genitalnoj regiji - prikaz slučaja. Serbian Journal of Dermatology and Venereology. 2013;2(3):106-9.

23. Souza CF, Thomé EP, Menegotto PF, Schmitt JV, Shibue JR, Tarlé RG. Topography of basal cell carcinoma and their correlations with gender, age and histologic pattern: a retrospective study of 1042 lesions. An Bras Dermatol. 2011;86(2):272-7.

24. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol. 2002;147(1):41-7.

25. Sexton M, Jones DB, Maloney ME. Histologic pattern analysis of basal cell carcinoma. Study of a series of 1039 consecutive neoplasms. J Am Acad Dermatol. 1990;23(6 Pt 1):1118-26.

26. Saldanha G, Fletcher A, Slater DN. Basal cell carcinoma: a dermatopathological and molecular biological update. Br J Dermatol. 2003;148(2):195-202.

27. Pyne JH, Myint E, Barr EM, Clark SP, Hou R. Basal cell carcinoma: variation in invasion depth by subtype, sex, and anatomic site in 4,565 cases. Dermatol Pract Concept. 2018;8(4):314-9.

28. Ciążyńska M, Sławińska M, Kamińska-Winciorek G, Lange D, Lewandowski B, Reich A, et al. Clinical and epidemiological analysis of basosquamous carcinoma: results of the multicenter study. Sci Rep. 2020;10(1):18475.

29. Tatalović V, Bjelan S, Zeljković D, Marinković M, Višnjevac Lj, Jovanović M. From neglect to metastasis: a giant abdominal basal cell carcinoma. Med Pregl. 2024;77(9-12):344-7.

30. Dourmishev LA, Rusinova D, Botev I. Clinical variants, stages, and management of basal cell carcinoma. Indian Dermatol Online J. 2013;4(1):12-7.

31. Bøgelund FS, Philipsen PA, Gniadecki R. Factors affecting the recurrence rate of basal cell carcinoma. Acta Derm Venereol. 2007;87(4):330-4.

32. Mc Loone NM, Tolland J, Walsh M, Dolan OM. Follow-up of basal cell carcinomas: an audit of current practice. J Eur Acad Dermatol Venereol. 2006;20(6):698-701.

33. Dusingize JC, Olsen CM, Pandeya NP, Subramaniam P, Thompson BS, Neale RE, et al. Cigarette smoking and the risks of basal cell carcinoma and squamous cell carcinoma. J Invest Dermatol. 2017;137(8):1700-8.

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ESTIMATION OF THE TIBIAL LENGTH AND DEGREE OF TIBIAL TORSION

ODREĐIVANJE DUŽINE GOLENJAČE I STEPENA TIBIJALNE TORZIJE

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Abstract

Introduction. The tibia is a long, massive bone of the lower leg, the length of which is used in anthropological analyses to estimate body height. This bone is slightly rotated around its longitudinal axis, a condition known as tibial torsion. This study aimed to determine the total length of the tibia and the angle of tibial torsion, and to establish whether differences existed between right and left bones. **Material and Methods.** A total of 42 tibias from the osteological collection of the Department of Anatomy, Faculty of Medicine in Novi Sad were analysed (19 right, 23 left). Measurements of tibial length and the degree of torsion were performed, after which the measured values were compared to determine whether differences existed between right and left bones. **Results.** The average length of all bones was 37.45 cm, and the average value of the torsion angle was 28.68°. No statistically significant difference in length between right and left tibias was found, whereas the difference in the degree of torsion was statistically significant (t = 2.5690, p = 0.0141). Internal torsion was not recorded; in five tibias the angle of external torsion was over 40°, and in three cases it was exactly at the borderline value of 40°. **Conclusion.** No correlation was found between tibial length and the degree of tibial torsion. The torsion values of the tibias in the majority of the sample correspond to the most commonly described physiological range in the population.
Key words: Tibia; Torsion Abnormality; Anthropometry; Lower Extremity.

Sažetak

Uvod. Golenjača predstavlja dugu i masivnu kost potkolenice, čija se dužina koristi u antropološkim analizama za procenu telesne visine. Ova kost je blago rotirana oko svoje uzdužne osovine što se definiše kao tibijalna torzija. Cilj ovog istraživanja bio je određivanje ukupne dužine golenjače i ugla tibijalne torzije, kao i utvrđivanje razlike između desnih i levih kostiju. **Materijal i metode.** Analizirane su ukupno 42 golenjače iz osteološke kolekcije Zavoda za anatomiju Medicinskog fakulteta Novi Sad (19 desnih, 23 leve). Izvršena su merenja dužine golenjače i stepena njene torzije, a potom su izmerene vrednosti poređene, kako bi se utvrdilo da li postoje razlike između desnih i levih kostiju. **Rezultati.** Prosečna dužina svih kostiju iznosila je 37,45 cm, a prosečna vrednost ugla torzije 28,68°. Nije utvrđena statistički značajna razlika u dužini između desnih i levih golenjača, dok je razlika u stepenu torzije bila statistički značajna (t = 2,5690, p = 0,0141). Unutrašnja torzija nije zabeležena; kod pet golenjača ugao spoljašnje torzije bio je preko 40°, a u tri slučaja je iznosila graničnih 40°. **Zaključak.** Nije utvrđena povezanost između dužine golenjača i stepena tibijalne torzije. Vrednosti torzije golenjača kod većine uzoraka odgovaraju najčešće opisanom fiziološkom opsegu u populaciji.
Ključne reči: tibija; torzija; antropometrija; donji ekstremiteti

Introduction

The tibia is a paired, inner bone of the lower leg and is a long bone. It has a shaft, a proximal end, and a distal end. There are three surfaces on the tibial shaft: lateral, medial, and posterior. The upper end is massive and consists of the medial and lateral condyles that articulate with the femur, and on the lateral surface of the proximal end, there is an articular surface for articulation with the proximal end of the fibula. The front of the upper end has a bulge called a tibial tuberosity. The distal end is smaller, in the shape of a four-sided pyramid whose lateral side serves to articulate with the distal end of the fibula. The medial side of the lower end extends downwards into a massive bony process called the medial malleolus [1].

A person's height may be approximated by applying anthropological equations derived from the total length of the tibia [2]. The length of the tibia is important for determining a person's height. However tibial length and torsion are largely independent traits. It is used in anthropology and forensic medicine [3]. Height assessment can be done using anatomical or mathematical methods. The former is applicable to live specimens, while the latter is preferable where the specimen consists only of body parts or corpses [4].

The total tibial length is defined as the linear distance extending from the articular surface of the lateral condyle to the apex of the medial malleolus [5].

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Tibial torsion is described as the rotational alignment of the tibia around its longitudinal axis. It increases with age until maturity [6].

Tibial torsion was first described by Le Damany [7]. Tibial torsion refers to any deviation or twisting of the tibia around its longitudinal axis [8]. Numerous clinical, anthropometric, and radiological studies were conducted to determine tibial torsion. The authors of these studies used different methods on the upper and lower edges of the tibia [6,9–12].

There are internal and external torsions. Internal tibial torsion represents the least complex of the three torsional conditions. This condition is characterised by inward rotation of the tibia and is the most frequent cause of intoeing in children between one and three years of age. It commonly affects both lower limbs and typically resolves spontaneously by six years of age. In infants, the mean internal tibial rotation is approximately 5° (range: –30° to +20°), while children aged eight years and above generally demonstrate a mean external rotation of about 10° (range: –5° to +30°) [13,14]. External tibial torsion is characterised by an outward orientation of the ankle joint, leading to pronation, eversion, and the development of *pes planus*. It generally does not resolve spontaneously during growth. Nevertheless, it does not necessitate surgical correction by osteotomy [13].

The authors have established that the baseline value of rotation is 0 degrees (when both ankles are in the frontal plane). Internal torsion is not physiological. It disturbs normal gait and is marked with negative values, while external torsion is physiological (0-40°) and is marked with positive values, and anything over 40° represents a pathological finding [15].

During a child's growth and development, the angle of tibial torsion changes. The intrauterine legs are limited in position by the uterus, and the pressure of the uterine wall can cause the bones to twist [16].

Fetal movements are important for normal musculoskeletal development [17]. Physiological tibial torsion is oriented externally along the proximodistal axis and progressively increases with advancing age [6]. Tibial torsion is minimal or absent at birth. It increases to 15–25° by approximately eight years with neuromotor activity [18]. Tibial torsion demonstrates substantial interindividual variability and contributes to the development of femoral torsion [19].

This study aimed to determine the total length of the tibia and the angle of tibial torsion, and to determine whether there is a difference between the right and left bones.

Material and Methods

The sample consisted of 42 tibias obtained from the Department of Anatomy of the Faculty of Medicine, University of Novi Sad. Out of the total 42 tibias, there were 19 right and 23 left tibias. Tibial length and torsion were measured for all bones, followed by a comparative analysis between the right and left sides. Tibial length was measured in 42 specimens, whereas the torsion angle was measured in 41, as one tibia was damaged at the proximal end and could not be assessed. The study was conducted in accordance with the ethical principles and approved by the Ethics Committee of the Faculty of Medicine, University of Novi Sad (approval number: 01-39/46).

All bones were photographed using an iPhone 14 Pro Max (Apple Inc., Cupertino, CA, USA) with a resolution of 12 MP (4032 x 3024 pixels) under standardised conditions. Each tibia was placed on a horizontal platform covered with a surgical compress. The bone was positioned with its posterior surface in contact with the platform, while the anterior border was oriented superiorly. The posterior surfaces of the medial and lateral condyles were in contact with the platform, providing a stable position of the specimen. At the distal end, the posterior surface of the distal tibial extremity was in contact with the platform, while the medial malleolus did not touch the platform. The specimens were aligned along their longitudinal axis, ensuring clear visualisation of anatomical landmarks and accurate morphometric measurements.

The length of the bones was measured using the ImageJ 1.48v program, from the intercondylar eminence to the apex of the medial malleolus at the lower end (**Figure 1**). After calibration of the images using the *Set Scale* function, tibial length was measured using the *Straight Line Tool*, and the obtained values were recorded using the *Measure command*.

The torsion angle was measured with a universal transparent plastic goniometer (Bauerfeind, Germany) with a 360° circular scale and integrated centimetre ruler. The method of measuring using a goniometer involves placing the bone on a flat surface, with its condyles (upper end) resting on it. The lower ends of the bones will form a certain angle (relative to the upper end, with the condyles resting on the flat surface of the table) that can be measured using a goniometer. The arms of the goniometer are positioned so that one arm is parallel to the edge of the table, and the other arm overlaps the line extending between the midpoint of the medial malleolus of the tibia and the midpoint of the fibular incisure (**Figure 2**). Measured values were recorded in the protocol. All measurements were performed by the same observer. Absolute and relative

Figure 1. Measurement of the: A - length of the tibia; B - total tibial length (d), distance between articular surfaces (d_1)

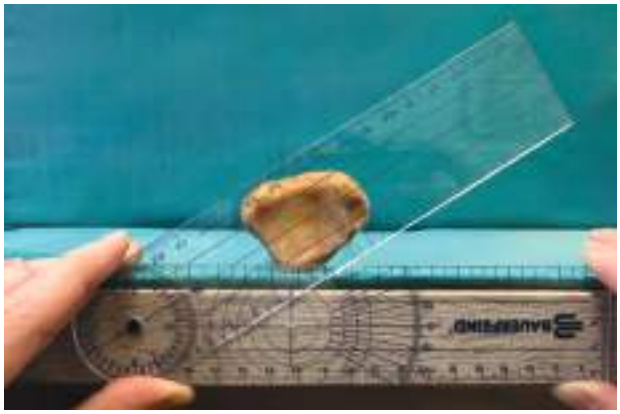

Figure 2. Measurement of tibial torsion

numbers were used, and statistical significance was assessed using Student's t-test. Measured values of tibial torsion (in degrees) were interpreted according to reference ranges from the literature [15], defining negative values as internal torsion, values between 0° and 40° as physiological external torsion, and values greater than 40° as pathological external torsion (**Figure 3).**

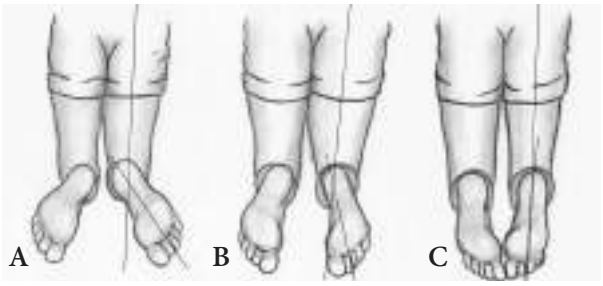

Figure 3. Tibial torsion: A - pathological external (above 40°); B - physiological external (0-40°); C - pathological internal (less than 0°)

Results

The mean tibial length for the entire sample was 37.45 cm, with a mean torsion angle of 28.68°. Tibial length was measured in 42 specimens, whereas the torsion angle was measured in 41, as one tibia was damaged at the proximal end and could not be assessed.

Among the 23 left tibias, the mean length was 37.34 cm (SD = 2.49 cm) and the mean torsion angle was 25.43° (SD = 9.82°). In the 19 right tibias, the mean length was 37.59 cm (SD = 2.74 cm) and the mean torsion angle was 32.83° (SD = 8.21°).

Figure 4 presents the mean tibial torsion values for the right and left sides. No statistically significant difference was observed in tibial length between sides (t = 0.3101, p = 0.758). In contrast, the difference in torsion angle between right and left tibias was statistically significant (t = 2.5690, p = 0.014).

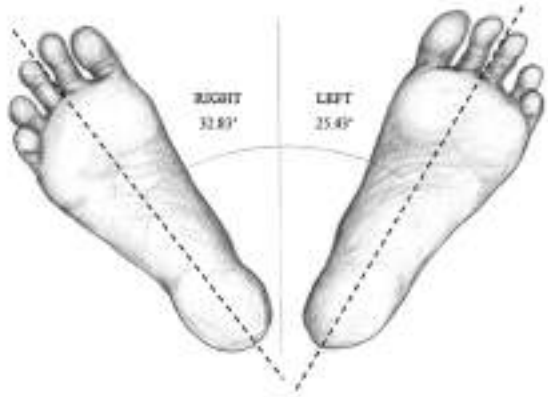

Figure 4. Average tibial torsion values (right and left side)

Among the total number of bones, external torsion angles greater than 40° were recorded in five cases: four in right tibias and one in a left tibia. In three additional cases, the external torsion angle reached the threshold value of 40° (**Figure 5**).

Figure 5. Distribution of tibial torsion patterns according to body side

Table 1. Descriptive analysis of the left and right tibial length

	Min (cm)	Max (cm)	x ±SD (cm)	p
Left	31	41.9	37.34 ± 2.49	0.758
Right	30.6	40.5	37.59 ± 2.74	

Min - minimal value, Max - maximal value, SD - standard deviation, p<0.05

Table 2. Descriptive analysis of the left and right tibial torsion

	Min (°)	Max (°)	x ±SD (°)	p
Left	10	46	25.43 ± 9.82	0.014
Right	25	50	32.83 ± 8.21	

Min - minimal value, Max - maximal value, SD - standard deviation, p<0.05

No cases of internal torsion or torsion with a baseline value of 0° were observed.

The ranges of tibial length and torsion angle are presented in **Tables 1 and 2**.

Discussion

Over the past two decades, studies conducted in Serbia have reported methods for estimating stature based on measurements of the long bones of the limbs [20,21].

Previous research has demonstrated sex-related differences in mean tibial length. The average length of the tibia in males ranges from 37 to 41 cm, while in females it ranges from 35 to 38 cm, in accordance with population differences [21–24].

Due to insufficient data, it was not possible to determine the sex of the person to whom the tibia belonged in our study. The mean tibial length measured in our study was 37.45 cm, which is in agreement with previously published findings [21–25].

It should be noted that estimated calculated heights based on the mean tibial length are not entirely precise, as the mean tibial length was applied without consideration of sex.

Most authors have observed that in humans, the most common external tibial rotation is between 10 and 30° [16,26–28].

According to our results, the measured torsion values in 25 cases (60.98%) fell within this interval, and in 16 cases (39.02%) exceeded it.

In a cadaveric study by Villamin et al. [29], conducted on 28 limbs of Filipino adults, the average value of tibial torsion was 28.9° ± 10.8°, with a range of 10° to 50°. The obtained values are comparable, although the methodologies differ, primarily in the choice of anatomical reference points and the approach to establishing the proximal and distal tibial axes. The average value of tibial torsion in our sample is identical to the value obtained in the mentioned study, without internal torsion.

It has been observed that right tibias tend to show greater external torsion, while internal torsion, where present, occurs more frequently on the left side [REF]. Similar results were obtained in our study, in which the angle of external torsion was significantly greater on the right side.

Based on tibial length, body height can be estimated using *the anthropological formula* proposed by Trotter and Gleser (1952, 1958): for women, $h = 72.572 + 2.533*T$; for men, $h = 81.688 + 2.392*T$, where h denotes the estimated stature in centimetres, and T represents tibial length in centimetres, and T represents tibial length (cm). The regression coefficients (2.533 and 2.392) expresses the contribution of tibial length to the predicted stature, whilst the constant (72.572 and 81.688) represents the intercept of the equation, corresponding to the theoretical stature value when tibial length equals zero [30–32].

Similar results were obtained in our study because the angle of external torsion is significantly larger on the right side.

In a CT-based study by Gallo et al. [33], the average value of tibial torsion was 27.5 ± 8.3°, with pronounced individual variability and frequent differences between the left and right sides. In our sample, the average value of tibial torsion was 28.68°, which is very close to the values reported by Gallo et al. Also, in both studies, asymmetry between the right and left sides was observed, with a higher degree of external torsion of the right tibia.

Pronounced tibial torsion may be associated with clinical manifestations involving the knee, including anterior knee pain, gait disturbances, and patellar instability [34].

The tibial torsion values observed in the present study fall within the physiological range reported in the literature and are consistent with the findings of Hawi et al. [35]. A statistically significant side-related difference was identified, with greater external torsion in the right tibia, in line with previously reported lateral asymmetry in tibial rotation.

Tibial torsion is almost always corrected by growth. Previously, various splints, corsets, and special shoes were used to correct torsion. However, none of this is an effective therapeutic modality [36].

Operative treatment may be indicated in patients above eight years of age when significant functional or aesthetic deformity is present, particularly in cases of anteversion greater than 50° and internal rotation exceeding 80° [37]. Patients aged 13-17 years experienced significantly longer hospitalisation and a longer time from admission to surgery compared with those under 13 years ($p<0.05$) [38].

According to our results, external torsion would be a much more common indication for surgical treatment. No cases of internal torsion were recorded, and external pathological torsion was observed in five cases. Given that these were adult bones, all five cases would be candidates for rotational osteotomy.

Several limitations of this study should be considered. These include the relatively small sample size and the measurement methodology, as digital measurements performed using specialised software may provide greater precision. Additionally, the lack of information on the age and sex of the individuals, as well as the inability to match left and right tibias from the same individual, may have influenced the interpretation of the results.

Conclusion

Analysis of the sample revealed a mean tibial length of 37.45 cm, with slightly higher values observed on the right side (37.59 cm) compared to the left (37.34 cm). The overall mean tibial torsion was 28.68°, with mean values of 32.83° in the right tibias and 25.43° in the left tibias. Pathological external tibial torsion (>40°) was more frequently identified on the right side (right: 4 cases; left: 1 case).

No association was found between tibial length and the degree of torsion. In 60.98% of cases, the measured tibial torsion values fell within the range most commonly reported in the literature as prevalent in the general population.

References

1. Bourne M, Sinkler MA, Murphy PB. Anatomy, bony pelvis and lower limb: tibia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2026 Jan 19]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526053/
2. Saknure MB, Waghmare CS. Estimation of human height by measuring length of tibial bone. Eur J Cardiovasc Med. 2025;15(4):93-6.
3. Elijah SO, Peter AI, Ekanem AU, Edet IE, Oyakhire MO. Estimating tibia length: an anatomical landmarks evaluation of bones and X-ray radiographs. Asian Journal of Medicine and Health. 2022;20(4):42-54.
4. Banyeh M, Abdulai AR, Shittu SO, Osei EE, Poku EO, Adinyira Komla AA. Sex and height estimation using percutaneous ulna and tibia length in a Ghanaian population: new data and a test of published equations. Forensic Sci Int Rep. 2022;6:100284.
5. Lynch JJ, Maijanen H, Prescher A. Analysis of three commonly used tibia length measurement techniques. J Forensic Sci. 2019;64(1):181-5.
6. Stephen JM, Teitge RA, Williams A, Calder JDF, El Daou H. A validated, automated, 3-dimensional method to reliably measure tibial torsion. Am J Sports Med. 2021;49(3):747-56.
7. Le Damany P. La torsion du tibia: normale, pathologique, experimentale. J Anat Physiol (Paris). 1909;45:598-615.
8. Snow M. Tibial torsion and patellofemoral pain and instability in the adult population: current concept review. Curr Rev Musculoskelet Med. 2021;14(1):67-75.
9. Borish CN, Mueske NM, Wren TAL. A comparison of three methods of measuring tibial torsion in children with myelomeningocele and normally developing children. Clin Anat. 2017;30(8):1043-8.
10. Edmonds EW, Parvaresh KC, Price MJ, Farnsworth CL, Bomar JD, Hughes JL, et al. The reliability of measurements for tibial torsion: a comparison of CT, MRI, biplanar radiography, and 3D reconstructions with and without standardized measurement training. J Pediatr Soc North Am. 2023;5(3):661.
11. Vertesich K, Chiari C, Zalaudek M, Hebenstreit K, Schneider E, Windhager R, et al. The bimalleolar method shows the most reliable results for measuring tibial torsion in rotational MRI. J Clin Med. 2025;14(13):4523.
12. Gavira N, Cochard B, Guanziroli N, Di Laura Frattura G, Dayer R, Ceroni D. A new method for assessing tibial torsion using computerized tomography in a pediatric population. Front Pediatr. 2024;12:1368820.
13. Putra PPAWK, Maharjana MA. Torsional deformity: a review article. International Journal of Research and Review. 2025; 12(9):12-8.
14. Kim S, Suzuki M, Minowa K, Nittono H, Shimizu T. Efficacy of a tibia counter rotator system for the treatment of internal tibial torsion in children. Children (Basel). 2022;9(7):970.
15. Hutter CG, Scott W. Tibial torsion. J Bone Joint Surg Am 1949;31(3):511-8.
16. Kristiansen LP, Gunderson RB, Steen H, Reikerås O. The normal development of tibial torsion. Skeletal Radiol. 2001;30(9): 519-22.
17. Verbruggen SW, Kainz B, Shelmerdine SC, Hajnal JV, Rutherford MA, Arthurs OJ, et al. Stresses and strains on the human fetal skeleton during development. J R Soc Interface. 2018;15(138):20170593.
18. Intoeing gait. In: Evans A. Pocket podiatry. Paediatrics. Edinburg: Churchill Livingstone/Elsevier; 2010. p. 183-205.
19. Grisch D, Dreher T. Torsionen und Torsionsentwicklung der unteren Extremität. Orthopade. 2019;48(6):523-30.
20. Marinković N, Vasić Vilić J. Correlation between the lengths of the long bones of the forearm and the fibula with body height in our population. Vojnosanit Pregl. 2012;69(5):394-8.
21. Gardasevic J. Standing height and its estimation utilizing tibia length measurements in adolescents from western region in Kosovo. Int J Morphol. 2019;37(1):227-31.

22. Aitken SA. Normative values for femoral length, tibial length, and the femorotibial ratio in adults using standing full-length radiography. Osteology. 2021;1(2):86-91.

23. Tiwari P, Datta A. Estimation of stature by measuring tibial length in young adults: a community-based approach. Indian Internet Journal of Forensic Medicine and Toxicology. 2023;20(3-4):66-71.

24. Mittino G, Langstaff H, García-Donas JG. Sex and stature estimation on the tibia: a virtual pilot study on a contemporary Hispanic population. J R Anthropol Inst. 2024;30(3):743-61.

25. Sherk VD, Bemben DA, Bemben MG, Anderson MA. Age and sex differences in tibia morphology in healthy adult Caucasians. Bone. 2012;50(6):1324-31.

26. Hicks J, Arnold A, Anderson F, Schwartz M, Delp S. The effect of excessive tibial torsion on the capacity of muscles to extend the hip and knee during single-limb stance. Gait Posture. 2007;26(4):546-52.

27. Mousavi H, Hosseini A, Rostami K, Shahrokh SG, Taravati AM, Jafari S, et al. Evaluation of incidence of tibial mal rotation after closed tibial intra-medullary nailing and its effects on clinical outcomes of the patients: a prospective study. Adv Biomed Res. 2025;14(1):19.

28. Duparc F, Thomine JM, Simonet J, Biga N. Femoral and tibial bone torsions associated with medial femoro-tibial osteoarthritis. Index of cumulative torsions. Orthop Traumatol Surg Res. 2014;100(1):69-74.

29. Villamin C, Syquia J. Tibial torsion among Filipinos: a cadaveric study. Malays Orthop J. 2012;6(3):27-30.

Rad je primljen 3. II 2026.
Recenziran 24. II 2026.
Prihvaćen za štampu 2. V 2026.
BIBLID.0025-8105:(2026):LXXIX:3-6:98-103.

30. Volkmar AJ, Stinner DJ, Pennings J, Mitchell PM. Prevalence of individual differences in tibial torsion: a CT-based study. J Am Acad Orthop Surg. 2022;30(2):e199-203.

31. Reikerås O, Høiseth A. Torsion of the leg determined by computed tomography. Acta Orthop Scand. 1989;60(3):330-3.

32. Staheli LT. Torsion - treatment indications. Clin Orthop Relat Res. 1989;(247):61-6.

33. Gallo MC, Tucker DW, Reddy A, Pannell WC, Heckmann N, Marecek GS. Large individual bilateral differences in tibial torsion impact accurate contralateral templating and the evaluation of rotational malalignment. J Orthop Trauma. 2021;35(8): e277-82.

34. Alexander N, Cip J, Studer K, Dobler F, Lengnick H, Payne E, et al. Does pathologically increased or decreased tibial torsion affect muscle activations during walking in typically developing adolescents? J Biomech. 2021;128:110727.

35. Hawi H, Kaireit TF, Krettek C, Liodakis E. Clinical assessment of tibial torsion differences. Do we always need a computed tomography? Eur J Trauma Emerg Surg. 2022;48(4):3229-35.

36. Knittel G, Staheli LT. The effectiveness of shoe modifications for intoeing. Orthop Clin North Am. 1976;7(4):1019-25.

37. Lincoln T, Suen P. Common rotational variations in children. J Am Acad Orthop Surg. 2003;11(5):312-20.

38. Topalović B, Mratinković I, Radulović B, Bjelobrk M, Milankov V. Treatment dynamics of tibial shaft fractures in children - the role of gender, age and treatment method. Med Pregl. 2024;77(5-6):165-70.

CONCENTRATION OF URIC ACID IN PATIENTS WITH BIPOLAR DISORDER

KONCENTRACIJA MOKRAĆNE KISELINE KOD PACIJENATA SA BIPOLARNIM POREMEĆAJEM

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Abstract

Introduction. Bipolar disorder represents a mood disorder whose aetiology and pathogenesis remain poorly understood. One proposed theory suggests a connection between this condition and uric acid, the final product of purine metabolism. Identifying measurable biomarkers for the prediction and diagnosis of bipolar disorder could open new avenues for a deeper understanding of not only this condition but also psychiatric disorders in general. The aim of this study was to investigate whether a statistically significant association exists between the different phases of bipolar disorder and uric acid concentrations. **Material and Methods.** This retrospective study included all patients hospitalised over the past two years at the Clinic for Psychiatry in Novi Sad with a diagnosis of bipolar disorder. Using data extracted from patient medical records, uric acid concentrations were analysed and compared between patients in manic and depressive phases. **Results.** A total of 103 patients were included in the analyses, of whom 27.18% (n = 28) were male, and 72.82% (n = 75) were female. The mean duration of psychiatric treatment was 10.62 years. Of the total sample, 43.69% (n = 45) of patients were in the manic phase, whilst 56.31% (n = 58) were in the depressive phase of bipolar disorder. The mean uric acid concentration in the manic phase was 342.62 μmol/l ± 105.62, compared to 320.24 μmol/l ± 97.81 in the depressive phase. **Conclusion.** No statistically significant association was found between the uric acid concentration and the phase of bipolar disorder.

Key words: Bipolar Disorder; Depression; Mania; Uric Acid; Purines; Biomarkers

Sažetak

Uvod. Bipolarni poremećaj predstavlja poremećaj raspoloženja čija su etiologija i patogeneza nerazjašnjene. Postoji teorija o povezanosti ove bolesti sa mokraćnom kiselinom kao poslednjom destinacijom u metabolizmu purina. U slučaju pronalaženja merljivih biomarkera za predikciju i dijagnostikovanje, otvorili bismo vrata ka dubljem razumevanju ne samo bipolarnog, već i psihijatrijskih poremećaja uopšte. Cilj je bio ispitati da li postoji statistički značajna povezanost između različitih faza bipolarnog poremećaja i koncentracije mokraćne kiseline. **Materijal i metode.** Ovom retrospektivnom studijom obuhvaćeni su svi pacijenti koji su u poslednje dve godine bili hospitalizovani u Klinici za psihijatriju u Novom Sadu pod dijagnozom bipolarnog poremećaja. Pomoću podataka uzetih iz kliničkog informacionog sistema, analizirane su koncentracije mokraćne kiseline kod pacijenata sa maničnim i kod pacijenata sa depresivnim fazama. **Rezultati.** U ovoj studiji smo pratili 103 pacijenta, od kojih su 27,18% (28/103) muškog, a 72,82% (75/103) ženskog pola. Prosečno trajanje psihijatrijskog tretmana iznosilo je 10,62 godine. U maničnoj fazi bilo je 43,69% (45/103) pacijenata, dok je 56,31% (58/103) bilo u depresivnoj fazi bipolarnog poremećaja. Koncentracija mokraćne kiseline pacijenata u maničnoj fazi iznosila je u proseku 342,62 ± 105,62 μmol/l, a u depresivnoj fazi 320,24 ± 97,81 μmol/l. **Zaključak.** Nije ustanovljena statistički značajna povezanost između koncentracije mokraćne kiseline i faza bipolarnog poremećaja.

Ključne reči: bipolarni poremećaj; depresija; manična faza; mokraćna kiselina; purini; biomarkeri

Introduction

Bipolar disorder, formerly known as manic-depressive psychosis (MDP), is a chronic mental illness classified among mood disorders. It is characterised by recurrent episodes of mania, depression, and mixed states that alternate over varying time periods [1].

Approximately two per cent of the global population is affected by this condition, making it one of the most prevalent mental illnesses worldwide [2]. Onset typically occurs in the third decade of life [1]. Individuals with bipolar disorder have a significantly higher mortality rate and a lifespan of 10-20 years shorter than that of the general population [3]. Whilst increased rates of cardiovascular disease and comorbid substance use disorders contribute to this, suicide remains the leading cause of death [1]. Despite the availability of effective treatment, the interval between disease onset and diagnosis is often prolonged, averaging approximately six years [4].

Early diagnosis remains a considerable challenge in clinical practice, as bipolar disorder frequently presents initially as a depressive episode that is clinically indistinguishable from unipolar depression. This is significant because misdiagnosing bipolar disorder as depression may result in the prescription of antidepressants without mood stabilisers, which carries a risk of triggering a switch to hypomania or mania [5].

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Abbreviations
MDP – manic-depressive psychosis
GABA – gamma-aminobutyric acid

As more information has been gathered on the epidemiology of bipolar disorder, it has become increasingly evident that some patients do not experience full manic episodes, yet exhibit noticeable elevations in mood (hypomania). This gave rise to the classification of the disorder into Type I (mania ± depression) and Type II (hypomania ± depression) [5].

On average, a manic episode lasts three to four months, whilst a depressive episode lasts four to six months [1]. The core triad of manic symptoms comprises: (1) emotional disturbance (euphoric or irritable mood), (2) psychomotor symptoms and signs (hyperactivity), and (3) expansive or inflated self-esteem and self-confidence (cognitive symptoms) [6]. By contrast, the hallmark features of depression are loss of interest and pleasure in all activities (anhedonia) [1,6].

Despite numerous studies, the aetiology of bipolar disorder remains poorly understood. Genetic factors are considered the principal cause, with environmental influences thought to act as triggers [7].

Several theories have been proposed to explain the mechanisms underlying the onset of bipolar disorder. One hypothesis suggests that purinergic dysfunction plays a role in the pathophysiology of mood disorders and other psychiatric conditions [8]. Purines are central to neurotransmission and neuromodulation, influencing the activity of several neurotransmitters, including dopamine, gamma-aminobutyric acid (GABA), glutamate, and serotonin [8,9]. A growing body of evidence supports the involvement of the purinergic system in mood regulation, motor activity, cognitive function, sleep, and behaviour [10]. Consequently, research attention has turned to uric acid, the end product of purine metabolism [11].

The relationship between bipolar disorder and uric acid has been a subject of discussion since the early days of psychiatry. In the latter half of the nineteenth century, Danish physician Karl Lange introduced the concept of "uric acid diathesis" in the pathogenesis of depression – the notion that mental disorders may arise from imbalances in uric acid levels [11]. In 1921, German psychiatrist Emil Kraepelin described associations between manic symptoms, uric acid excretion, hyperuricaemia, and gout [12]. Later, in 1949, psychiatrist John Cade proposed that a condition involving uric acid was responsible for the "psychotic excitement" observed in his manic patients [13]. Since the 1960s, certain psychological traits, including disinhibition, hyperthymic temperament, impulsivity, and excitement seeking, have been associated with elevated uric acid levels [11].

Uric acid is thought to contribute to the pathogenesis of bipolar disorder through oxidative stress and other mechanisms [7]. Elevated uric acid levels are associated with accelerated purinergic transformation and reduced adenosine transmission. It has been hypothesised that reduced adenosine activity, principally at the A1 receptor level – accompanied by correspondingly elevated uric acid levels - disrupts neurotransmitter pathways and is associated with manic behaviour [14].

Several studies suggest that impairment of the purinergic system plays a role in the pathophysiology of mood disorders, including both bipolar disorder and unipolar depression [15]. Uric acid levels and impulsivity have both been found to be elevated in bipolar disorder, with increased impulsivity showing a positive correlation with higher uric acid levels [16]. Research also indicates that serum uric acid levels may serve as prognostically accurate biomarkers for identifying depressive patients at risk of conversion to bipolar disorder [4,7].

Further support for a link between bipolar disorder and uric acid comes from the antimanic and antipsychotic effects of allopurinol, a xanthine oxidase inhibitor that reduces uric acid synthesis [17,18]. Given that psychiatry currently lacks clinically validated biomarkers for predicting and diagnosing bipolar disorder, further investigation into the role of uric acid in its pathogenesis is of considerable importance. A deeper understanding of this condition may help address the problem of delayed diagnosis and, in turn, pave the way for more effective treatment.

This study aimed to examine whether a statistically significant correlation exists between different phases of bipolar disorder and uric acid levels.

The hypothesis proposed was that uric acid levels are higher in patients experiencing a manic episode than in those in the depressive phase of bipolar disorder.

Material and Methods

A retrospective study was conducted and approved by the Ethics Committee of the University Clinical Center of Vojvodina, Novi Sad (reference number 00-1141/8; date: 1.12.2023). The study included adult patients hospitalised at the Clinic for Psychiatry in Novi Sad during 2021 and 2022, who carried a confirmed diagnosis of bipolar disorder.

Data were obtained from medical records stored in the clinical information system and subsequent-

Table 1. Demographic characteristics of the patients

Characteristic	Manic phase (n=45)	Depressive phase (n=58)	Total (n=103)	P-value
Mean age, years (mean±SD)	44.45±13.91	42.84±15.84	43.39±14.65	0.493
Sex, n (%)				
Male	13 (28.89)	15 (25.86)	28 (27.18)	0.824
Female	32 (71.11)	43 (74.14)	75 (72.82)	
Average age, (mean ± SD)				
Men	41.38±13.23	45.6±18.15	43.64±15.91	0.678
Women	45.22±13.37	41.88±15.07	43.31±14.37	0.324
Level of education, n (%)				
Elementary school	0 (0)	1 (1.72)	1 (0.97)	1.000
Secondary school	6 (13.33)	14 (24.14)	20 (19.42)	0.743
Higher Education Diploma	0 (0)	3 (5.17)	3 (2.91)	0.539
University	7 (15.56)	10 (17.24)	17 (16.50)	0.322

n – number of patients, SD – standard deviation; p – statistical significance

ly categorised and systematised using Microsoft Excel. Uric acid levels measured as part of routine laboratory analyses conducted during hospitalisation were the primary outcome of interest. These were compared between two defined patient groups: those in the depressive phase and those in the manic phase of bipolar disorder. Demographic data including sex, age, marital status, number of children, family history, number of previous hospitalisations, duration of treatment, age at disease onset, and use of alcohol and/or psychoactive substances were also recorded.

The distribution of numerical data was assessed using the Shapiro-Wilk test. Continuous variables with a normal distribution were compared using an unpaired Student's T-test, whilst the Mann-Whitney U test was applied to variables without a normal distribution. Categorical variables were compared using Fisher's exact test, and the Pearson's Goodness-of-fit χ^2 test was used to compare the manic and depressive phase groups. A p-value of less than 0.05 was considered statistically significant.

Statistical analyses were performed using JASP Team (2025). JASP (Version 0.19.3) [computer software].

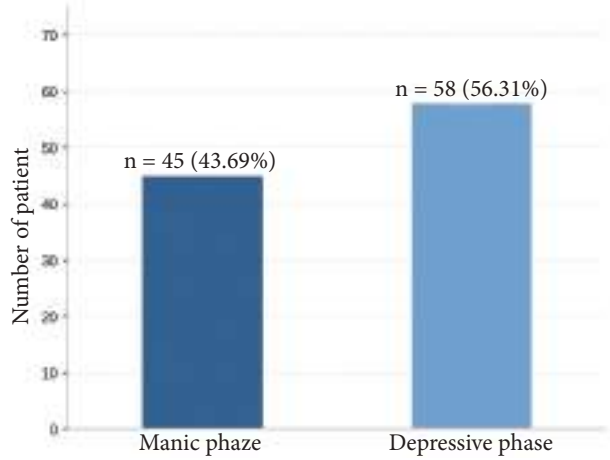
Results

A total of 103 patients were included in this study, of whom 27.18% (n = 28) were male and 72.82% (n = 75) were female. The mean age of the cohort was 43.39±14.65 years; the mean age for male patients was 43.64±15.91 years and for female patients 43.31±14.37 years. With regard to educational attainment, 19.42% (n = 20) had completed secondary school, 16.50% (n = 17) had completed university education, 2.91% (n = 3) had completed higher education, and 0.97% (n = 1) had completed primary school only **(Table 1).**

A positive psychiatric family history was recorded in 32.03% (n = 33) of patients. A total of 26.21% (n = 27) of patients reported use of psychoactive substances and/or alcohol. The mean duration of psychiatric treatment was 10.62±9.82 years. No statistically significant difference was observed in uric acid levels between patients in the manic phase (342.62±105.62 μmol/L) and those in the depressive phase of bipolar disorder (320.24±97.81 μmol/L) (p = 0.2686) **(Table 2).**

No statistically significant associations were identified between the demographic or clinical characteristics of the patients and a specific phase of bipolar disorder.

The distribution of patients between the manic phase (43.69%, n = 45) and the depressive phase (56.31%, n = 58) did not differ significantly **(Graph 1).**



Graph 1. Distribution of patients by phase of bipolar disorder

Table 2. Uric acid levels and clinical characteristics of patients

Characteristic	Manic phase (n=45)	Depressive phase (n=58)	Total (n=103)	P-value
Uric acid level, μmol/l (mean±SD)	342.62±105.62	320.24±97.81	330.02±100.91	0.269
Psychoactive substance abuse, n (%)	14 (31.11)	13 (22.41)	27 (26.21)	0.370
Psychiatric family history, n (%)	10 (22.22)	23 (39.66)	33 (32.03)	0.088
Average duration of treatment, (mean±SD)	13.86±9.29	10.65±9.13	10.62±9.82	0.143

n-number of patients, SD-standard deviation; p-statistical significance

Discussion

The present study found no statistically significant difference in uric acid concentrations between patients in the manic and depressive phases of bipolar disorder, nor any significant association between demographic or clinical characteristics and disease phase.

Whilst no statistically significant relationship between uric acid and the two phases was observed, further analysis reveals several noteworthy findings about the demographic characteristics of patients with bipolar disorder. With respect to sex distribution, female patients constituted the numerical majority, accounting for 72.82% of our sample. This figure is somewhat higher than the 62.8% reported by Chen et al. [3], though not unexpected, as previous studies have consistently demonstrated a higher prevalence of mood disorders - particularly depression - amongst women, occurring two to ten times more frequently than in men, depending on the specific disorder [19]. The prevailing explanation is that hormonal fluctuations, which are physiologically more pronounced in women due to the menstrual cycle, confer a greater susceptibility to these conditions [19,20]. An alternative explanation is that men are less likely to seek psychiatric help than women [21,22].

Beyond the lower prevalence in men, several authors have associated the manic phase and elevated uric acid concentrations more frequently with male patients, as confirmed by Muti et al. in their study (p=0.000) [11]. Our study did not replicate this finding (p=0.8243). This sex-related association may be related to specific behavioural patterns and lifestyle factors – such as physical activity levels and consumption of caffeine, nicotine, and alcohol as well as dietary habits - that occur more frequently in male patients during the manic phase and are known to elevate uric acid concentrations [22,23].

The mean age of patients diagnosed with bipolar disorder varies across studies, generally falling within the fourth to fifth decade of life [2,3,16]. The mean age reported by Albert et al. was 47.74 ± 15.48 years, which is broadly consistent with the mean of 43.39 ± 14.65 years in our cohort [2]. Insufficient data on age at disease onset precluded direct comparison with other studies; such a comparison, alongside age at the time of clinical presentation, would provide a more complete picture of the natural history of bipolar disorder. Nevertheless, the available data are consistent with the established finding that the first symptoms of bipolar disorder typically emerge in the third decade of life [1]. The mean age of hospitalised patients further reflects the well-documented delay between symptom onset and confirmed diagnosis.

Although no statistically significant association was found in our study between the use of psychoactive substances or alcohol and uric acid (p=0.3701), Sanli et al. investigated the effects of various substances on biochemical parameters and found that uric acid concentrations were lower in individuals using psychoactive substances compared to a control group (p=0.047) [23]. This was attributed in part to nutritional deficiencies amongst substance users, who frequently prioritised drug procurement over adequate nutrition. The co-occurrence of psychiatric disorders in this population is also relevant, as these can suppress appetite and substantially alter nutritional status, directly affecting protein metabolism and, consequently, uric acid levels.

These findings highlight that numerous everyday factors can influence uric acid metabolism – a complexity acknowledged by Chen et al. [7]. Such factors include diet, alcohol and caffeine consumption, psychoactive substance use, medication, and the presence of comorbid conditions that affect uric acid metabolism.

This study has three notable limitations: the relatively small and selected sample of patients hospitalised at the Clinic for Psychiatry in Novi Sad; incomplete data for several included patients; and the absence of a healthy control group. The influence of these factors may account for the failure to confirm the working hypothesis in the present study, notwithstanding the statistically robust findings reported by numerous other authors on this topic.

Further investigation into this subject remains essential. The role of uric acid in the pathogenesis of

bipolar disorder is well-supported, yet highly complex, given the interplay of both exogenous and endogenous factors that collectively influence an individual's mental state. A deeper understanding of this complexity will not only advance knowledge of bipolar disorder but also contribute to a broader understanding of psychiatric phenomena more generally.

Conclusion

Bipolar disorder is amongst the most prevalent chronic mental illnesses. Given the existing evidence linking this condition to uric acid metabolism, we proposed the working hypothesis that uric acid concentrations would be elevated in the manic phase relative to the depressive phase of bipolar disorder. However, no statistically significant difference was identified.

The limitations of the present study are likely to have influenced these results. As such, the putative role of purines in the aetiopathogenesis of bipolar disorder should not be discounted. Further research is warranted to generate new insights and a more complete understanding of this complex and clinically important issue.

References

1. Niraj A. A short textbook of psychiatry. 7th ed. New Delhi: Jaypee Brothers Medical Publishers (P) LTD; 2011.

2. Albert U, De Cori D, Aguglia A, Barbaro F, Bogetto F, Maina G. Increased uric acid levels in bipolar disorder subjects during different phases of illness. J Affect Disord. 2015;173:170-5.

3. Chen J, Chen H, Feng J, Zhang L, Li J, Li R, et al. Association between hyperuricemia and metabolic syndrome in patients suffering from bipolar disorder. BMC Psychiatry. 2018;18(1):390.

4. Dos Santos Oliveira PM, Santos V, Coroa M, Ribeiro J, Madeira N. Serum uric acid as a predictor of bipolarity in individuals with a major depressive episode. Bipolar Disord. 2019;21(3):235-43.

5. Gelder M, Andreasen N, Lopez-Ibor J, Geddes, editors. New Oxford textbook of psychiatry. 2nd ed. Oxford: Oxford University Press; 2012.

6. Nedić A, Živanović O, editors. Psihijatrija. 4th ed. Novi Sad: Medicinski fakultet Novi Sad; 2017.

7. Chen H, Sun F, Jin W. Study on association of serum uric acid levels with bipolar disorder: systematic review and meta-analysis in Chinese patients. Ann Gen Psychiatry. 2023;22(1):20.

8. Bartoli F, Crocamo C, Mazza MG, Clerici M, Carrà G. Uric acid levels in subjects with bipolar disorder: a comparative meta-analysis. J Psychiatr Res. 2016;81:133-9.

9. Bartoli F, Crocamo C, Gennaro GM, Castagna G, Trotta G, Clerici M, et al. Exploring the association between bipolar disorder and uric acid: a mediation analysis. J Psychosom Res. 2016;84:56-9.

10. Ortiz R, Ulrich H, Zarate CA, Machado-Vieira R. Purinergic system dysfunction in mood disorders: a key target for developing improved therapeutics. Prog Neuropsychopharmacol Biol Psychiatry. 2015;57:117-31.

11. Muti M, Del Grande C, Musetti L, Marazziti D, Turri M, Cirronis M, et al. Serum uric acid levels and different phases of illness in bipolar I patients treated with lithium. Psychiatry Res. 2015;225(3):604-8.

12. Kraepelin E. Manic-depressive insanity and paranoia. Edinburgh (UK): E. & S. Livingstone; 1921.

13. Shorter E. The history of lithium therapy. Bipolar Disord. 2009;11(Suppl 2):4-9.

14. Machado-Vieira R, Lara DR, Souza DO, Kapczinski F. Purinergic dysfunction in mania: an integrative model. Med Hypotheses. 2002;58(4):297-304.

15. Cheffer A, Castillo ARG, Corrêa-Velloso J, Gonçalves MCB, Naaldijk Y, Nascimento IC, et al. Purinergic system in psychiatric diseases. Mol Psychiatry. 2018;23(1):94-106.

16. Chatterjee SS, Ghosal S, Mitra S, Mallik N, Ghosal MK. Serum uric acid levels in first episode mania, effect on clinical presentation and treatment response: data from a case control study. Asian J Psychiatr. 2018;35:15-7.

17. Machado-Vieira R, Soares JC, Lara DR, Luckenbaugh DA, Busnello JV, Marca GL, et al. A double-blind, randomized, placebo-controlled 4-week study on the efficacy and safety of the purinergic agents allopurinol and dipyridamole adjunctive to lithium in acute bipolar mania. J Clin Psychiatry. 2008;69(8):1237-45.

18. Brunstein M, Ghisolfi ES, Ramos FL, Lara DR. A clinical trial of adjuvant allopurinol therapy for moderately refractory schizophrenia. J Clin Psychiatry. 2005;66(2):213-9.

19. Rainville JR, Hodes GE. Inflaming sex differences in mood disorders. Neuropsychopharmacology. 2019;44(1):184-99.

20. Savić A, Savanov B, Subić L, Popović D, Aleksandrić T, Knežević A. Are there any differences in pain thresholds during the menstrual cycle? Med Pregl. 2024;77(7-8):228-33.

21. Smith KLW, Matheson FI, Moineddin R, Dunn JR, Lu H, Cairney J, et al. Gender differences in mental health service utilization among respondents reporting depression in a national health survey. Health. 2013;5(10):1561-71.

22. Gagne S, Vasiliadis HM, Preville M. Gender differences in general and specialty outpatient mental health service use for depression. BMC Psychiatry. 2014;14:135.

23. Sanli DB, Bilici R, Suner O, Citak S, Kartkaya K, Mutlu FS. Effect of different psychoactive substances on serum biochemical parameters. Int J High Risk Behav Addict. 2015;4(2):e22702.

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COMPARISON OF COLLAGEN AND ELASTIC FIBRE DISTRIBUTION IN THE LUNGS OF PATIENTS WITH SARCOIDOSIS AND HYPERSENSITIVITY PNEUMONITIS – A PILOT STUDY

POREĐENJE DISTRIBUCIJE KOLAGENIH I ELASTIČNIH VLAKANA U PLUĆIMA BOLESNIKA SA SARKOIDOZOM I HIPERSENZITIVNIM PNEUMONITISOM – PILOT STUDIJA

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Abstract

Introduction. Sarcoidosis and hypersensitivity pneumonitis are common interstitial lung diseases whose histopathological appearances may overlap, particularly when only bronchial biopsy specimens are available. This study aimed to examine differences in the distribution of collagen and elastic fibres between sarcoidosis and hypersensitivity pneumonitis. **Material and Methods.** Thirty-one histopathological slides from patients with sarcoidosis and hypersensitivity pneumonitis were analysed. Samples were obtained by transbronchial or surgical biopsy. Additional histological sections were stained using Masson Trichrome and Orcein methods. Following laboratory processing, representative microphotographs of alveolar tissue were obtained, and software-based image analysis was used to determine the surface areas occupied by collagen and elastic fibres, as well as by epithelium and the remaining interstitium. Clinical characteristics, including age, sex, smoking status, and occupation, were also recorded. **Results.** A higher density and proportion of collagen fibres were observed in hypersensitivity pneumonitis ($p<0.05$). The mean area occupied by collagen fibres was 0.63 ± 0.40 mm^2 in hypersensitivity pneumonitis, compared with 0.35 ± 0.47 mm^2 in sarcoidosis. The collagen proportion was 48.79% in hypersensitivity pneumonitis and 32.01% in the sarcoidosis group. No statistically significant difference in the density or proportion of elastic fibres was observed between the two diseases. Correlation analysis demonstrated a positive association between collagen and elastic fibres in sarcoidosis (rho = 0.632; p = 0.024). Sarcoidosis samples showed better preservation of alveolar tissue. **Conclusion.** Collagen fibre distribution is more pronounced in hypersensitivity pneumonitis than in sarcoidosis, whereas no difference in elastic fibre distribution was found between the two conditions.

Key words: Sarcoidosis; Lung; Lung Diseases, Interstitial; Extracellular Matrix; Collagen; Elastic Tissue; Biopsy

Sažetak

Uvod. Sarkoidoza i hipersenzitivni pneumonitis su česte intersticijumske bolesti pluća kod kojih postoje sličnosti u patohistološkim uzorcima pogotovu kada su dostupne isključivo bronhobiopsije. Cilj rada je ispitati razlike u distribuciji kolagenih i elastičnih vlakana kod sarkoidoze i hipersenzitivnog pneumonitisa. **Materijal i metode.** Za potrebe ove studije analiziran je 31 patohistološki preparat bolesnika obolelih od sarkoidoze i hipersenzitivnog pneumonitisa. Uzorci koji su korišćeni dobijeni su transbronhijalnom ili hirurškom biopsijom. Na dodatnim histološkim rezovima preparati su bojeni metodama *Masson Trichrome* i *Orcein*. Nakon laboratorijske obrade na dobijenim preparatima su načinjene reprezentativne mikrofotografije alveolarnog tkiva. Softverskom obradom mikrofotografija dobijene su površina kolagenih/elastičnih vlakana, kao i površine epitela i ostatka intersticijuma, nakon čega je izvršena statistička analiza dobijenih podataka. U statističku analizu bile su uključene i kliničke karakteristike poput starosti, pola, pušačkog statusa i zanimanja. **Rezultati.** Dokazana je veća gustina i udeo kolagenih vlakana u patohistološkim uzorcima bolesnika sa hipersenzitivnim pneumonitisom. Prosečna vrednost površine koju su zauzimala kolagena vlakna kod hipersenzitivnog pneumonitisa iznosila je $0,63 \pm 0,40$ mm^2, dok je kod sarkoidoze iznosila $0,35 \pm 0,47$ mm^2. Udeo kolagena kod hipersenzitivnog pneumonitisa iznosio je 48,79%, dok je kod sarkoidoze iznosio 32,01%. Gustina i udeo elastičnih vlakana nisu pokazali statistički značajne razlike između ova dva oboljenja. Korelacionom analizom utvrđena je proporcionalnost u distribuciji kolagenih i elastičnih vlakana kod sarkoidoze ($p < 0,05$). Takođe, primećena je bolja očuvanost alveolarnog tkiva na uzorcima sa sarkoidozom. **Zaključak.** Distribucija kolagenih vlakana u hipersenzitivnom pneumonitisu je značajnije izražena u odnosu na sarkoidozu. Razlike u distribuciji elastičnih vlakana nisu nađene.

Ključne reči: sarkoidoza; pluća; intersticijalna plućna bolest; ekstracelularni matriks; kolagen; elastično tkivo; biopsija

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology, the diagnosis of which remains somewhat arbitrary, non-standardised, and often unreliable [1,2]. The principal histopathological feature indicative of sarcoidosis is the presence of aseptic, typically non-caseating granulomas, often distributed lymphatically along the bronchovascular bundles of the pulmonary tree [1,3].

Hypersensitivity pneumonitis (HP) is defined as "an inflammatory and/or fibrotic disease affecting

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Abbreviations

HP	– hypersensitivity pneumonitis
MGCs	– multinucleated giant cells
APCs	– antigen-presenting cells
HP group	– hypersensitivity pneumonitis – group
S group	– sarcoidosis - group
SB	– surgical biopsy
ACE	– angiotensin-converting enzyme
sIL	– 2R Soluble interleukin-2 receptor

the lung parenchyma and small airways, typically resulting from an immune-mediated reaction provoked by an overt or occult inhaled antigen in susceptible individuals" [4]. Histopathological changes in HP are characterised by a triad comprising cellular bronchiolitis, interstitial pneumonia, and poorly formed non-necrotising granulomas [5–7].

From a differential diagnostic perspective, HP is often confused with sarcoidosis in the absence of specific histopathological features [2]. Nonetheless, specific differences can help distinguish the two entities: compared with sarcoidosis, granulomas in HP are smaller, poorly formed, less well-circumscribed, centred on the airways, and more commonly associated with multinucleated giant cells [8].

Sarcoidosis-associated pulmonary fibrosis results from fibroblast activation and proliferation, leading to increased collagen synthesis and deposition in the context of prolonged, chronic granulomatous inflammation [9]. A more prominent presence of collagen and fibroblasts at the periphery of the granuloma indicates that fibrosis in sarcoidosis begins peripherally before extending towards its central regions [9,10].

The structure of a sarcoid granuloma comprises a core containing aggregates of macrophages and epithelioid cells, along with a smaller number of multinucleated giant cells (MGCs), and an outer rim composed predominantly of T-lymphocytes with a minor proportion of B-lymphocytes [11]. Sarcoid granuloma formation begins with the phagocytosis of an antigen by monocytes, which subsequently differentiate into antigen-presenting cells (APCs) – specifically, macrophages and/or dendritic cells [11]. The antigen is then presented to T-lymphocytes by APCs, which accumulate and differentiate into epithelioid cells [11]. These cells then organise into cellular clusters to form an immature granuloma, within which inflammatory signals drive the fusion of macrophages and monocytes/dendritic cells, ultimately resulting in the formation of MGCs [11,12]. In most patients with sarcoidosis, granulomas regress spontaneously within a few years; in a significant proportion of patients, however, the disease instead becomes chronic and progressive, characterised by persistent granulomas and the formation of fibrotic lesions [12].

Granulomas and isolated MGCs are also present in most cases of acute/subacute HP and may contain cholesterol crystals or Schaumann bodies [4,7]. Schaumann bodies are a significant histopathological finding in the differential diagnosis of HP, as they can occur in any persistent granuloma, whereas in granulomatous infections they are rare or absent [4]. According to Churg, these structures also occur considerably more frequently in HP than in sarcoidosis [4]. Granulomas in HP are frequently described as poorly defined, reflecting the absence of fine concentric rings of fibrosis characteristic of sarcoid granulomas [4,8].

According to several studies [5,11,12], the presence of poorly formed granulomas in the acute and subacute forms of HP, alongside well-formed granulomas in sarcoidosis, is a characteristic feature distinguishing biopsy samples from these two diseases. Although granuloma morphology and distribution are traditionally regarded as important diagnostic features, they are not always clearly distinct, and considerable overlap may occur between sarcoidosis and hypersensitivity pneumonitis [2]. The identification of new markers, such as the specific distribution of collagen and elastic fibres, could contribute to more precise histopathological diagnosis, which in turn has implications for selecting the appropriate therapeutic approach.

Material and Methods

This retrospective study was conducted following approval by the institutional Scientific and Ethics Committee (Decision Nos. 46-2/8, 43-1/8, and 91/4, dated January 22, 2026). A total of 31 histopathological lung biopsies retrieved from the archives were analysed. Specimens were divided into two groups: 18 specimens from patients with hypersensitivity pneumonitis (HP group), and 13 from patients with sarcoidosis (S group).

Histopathological Tissue Preparation

The analysis included specimens obtained via transbronchial and surgical biopsy, with histologic and clinical confirmation of sarcoidosis or hypersensitivity pneumonitis.

Additional histological sections were stained using Masson's trichrome and Orcein methods, both performed according to previously validated laboratory protocols.

The Orcein solution was prepared by dissolving 0.1 g of Orcein in 100 mL of 70% ethanol, adding 1.35 mL of hydrochloric acid and 0.65 mL of distilled water. Slides were first rinsed in distilled water, then incubated in the Orcein solution for 60 minutes. Fol-

lowing staining, they were rinsed in 70% ethanol and running tap water. Counterstaining was performed using Hematoxylin for two minutes, after which the slides were rinsed again with water. Dehydration was performed using a graded series of alcohols (96% and 100% ethanol), followed by final clearing in xylene.

Masson's trichrome staining was performed by first rinsing the slides in distilled water, then incubating them in preheated Bouin's solution at 60 °C. After incubation, the slides were washed under running tap water and stained with Weigert's hematoxylin for five minutes, then rinsed again under running tap water.

Cytoplasmic structures were stained with 0.5% acid fuchsin for five minutes, then briefly rinsed in distilled water and treated with 1% phosphomolybdic acid for four minutes. Following a further rinse in distilled water, the slides were stained with 2.5% aniline blue for five minutes. Finally, dehydration was carried out through a graded series of alcohols (96% and 100% ethanol), followed by clearing in xylene.

Digital Image Analysis

Following laboratory processing, a single microphotograph containing alveolar tissue was captured at 200x magnification for each transbronchial biopsy specimen; for surgical biopsy (SB) specimens, three randomly selected microphotographs were captured at 200x magnification. Images were processed using QuPath software, version 0.7.0 (https://qupath.github.io/). Using segmentation and machine-learning methods, the software was trained to quantify elastin- and collagen-positive pixels **(Figure 1).** All microphotographs were subsequently analysed using the same principles and identical parameters. Absolute values per unit area were obtained for the fibres under evaluation, the remaining lung parenchyma, and the background. In addition, the proportion of evaluated fibres relative to the remaining lung parenchyma was calculated, with the background excluded from the analysis.

Clinical Characteristics

Patient clinical characteristics were retrieved from the Institute's information system, which recorded smoking status, occupation, biopsy specimen, sampling method, age, and sex.

Statistical Analysis

Statistical analysis was performed using JASP software, version 0.95.4.0 (https://jasp-stats.org). The normality of the data distribution was assessed using the Shapiro-Wilk test. Nominal variables were compared using the chi-squared test. The Mann-Whitney U test was used to compare non-normally distributed variables, and the Student's t-test was used for normally distributed variables. Correlations between numerical variables - the density of collagen and elastic fibres, analysed both across the combined groups and separately within each group, as well as fibre density across the total sample in relation to age - were assessed using Spearman's correlation coefficient. To evaluate effect size for the Mann-Whitney U test, the rank-biserial correlation coefficient was used, with absolute values greater than 0.5 indicating a large effect size; for the Student's t-test, Cohen's d was used to estimate effect size. A p-value of <0.05 was considered statistically significant.

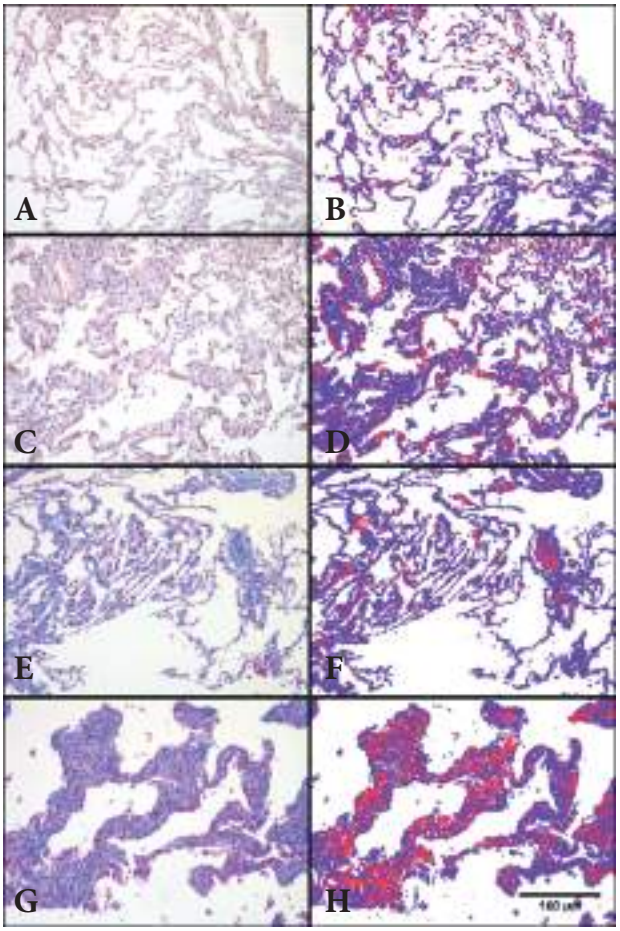
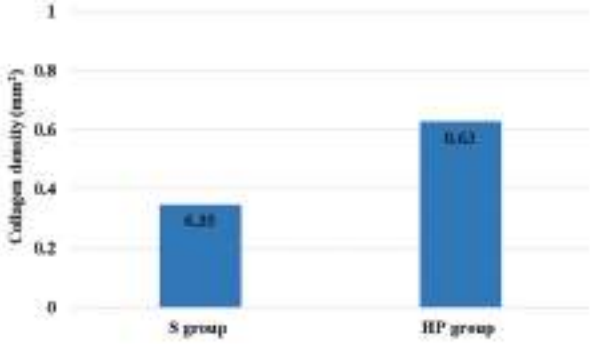


Figure 1. Display of segmentation and the result of pixel classification training for the purpose of quantifying the examined fibers; A and B – S group, Orcein, 200x; C and D – HP group, Orcein, 200x; E and F – S group, Masson's trichrome, 200x; G and H – HP group, Masson's trichrome, 200x.

Results

The mean age of patients in the S group was 49.15 years, compared with 56.77 years in the HP group; This difference was not statistically significant (t = 1.632; p = 0.113). Regarding sex distribution, a slightly higher proportion of females was observed in the



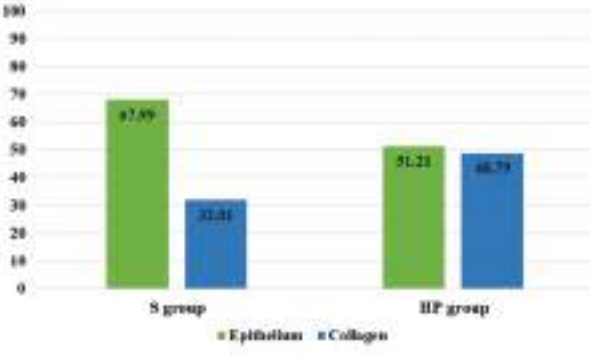
Graph 1. Collagen density across the study groups (U = 180.000; p = 0.018; rank-biserial = -0.539, 95% CI [-0.77, -0.182].

HP group. In contrast, male patients predominated in the S group, although this difference was not statistically significant (χ^2 = 1.454, p = 0.228). With respect to smoking status, 61.54% of participants in the S group were current or former smokers, compared with 38.89% in the HP group; conversely, non-smokers comprised 38.46% of the S group and 61.11% of the HP group**.** No statistically significant association was observed between disease group and smoking status (χ^2 = 1.551, p = 0.213).

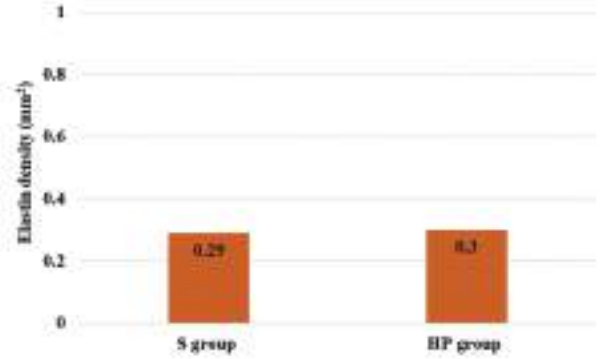
The most prevalent occupations were retirees (12.90%), homemakers (9.68%), and farmers (9.68%). Other occupations – including auto mechanic, economist, electrician, pharmacy technician, manual labourer, physiotherapist, hairdresser, tailor, nurse, painter, police officer, baker, security officer, salesperson, teacher, driver, and craftsman - were represented by only one or two patients, reflecting a heterogeneous distribution.

Bronchobiopsies and transbronchial biopsies accounted for a significantly higher proportion of the specimens (74.19%) than surgical biopsies (25.81%).

Analysis of collagen distribution revealed statistically significant differences between the groups. In terms of density, collagen was significantly more



Graph 2. Collagen-to-lung ratio between groups (U = 177.000, p = 0.016; rank-biserial correlation = -0.513)



Graph 3. Elastin density across the study groups (U = 133.000; p = 0.540; rank-biserial correlation = -0.137, 95% CI [-0.505, 0.274]).

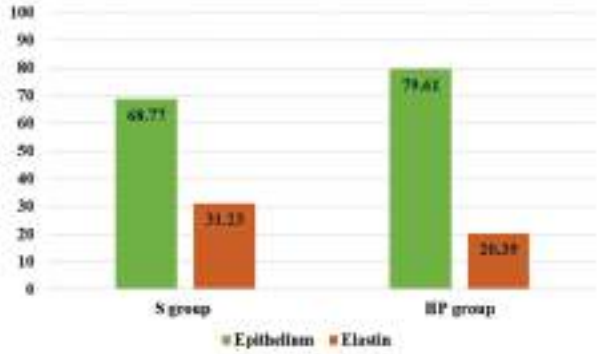
abundant in the HP group **(Figure 1, Graph 1).** The mean area occupied by collagen fibres was 0.63 ± 0.40 mm² in the HP group, compared with 0.35 ± 0.47 mm² in the S group (U = 180.000; p = 0.018; Rank biserial = -0.539, 95% CI [-0.77, -0.182].

Similar results were obtained for the proportion of collagen relative to the remaining tissue. In the HP group, collagen accounted for an average proportion of 48.79% **(Graph 2),** compared with a significantly lower average of 32.01% in the S group (U = 177.000, p = 0.016; rank-biserial correlation = -0.513).

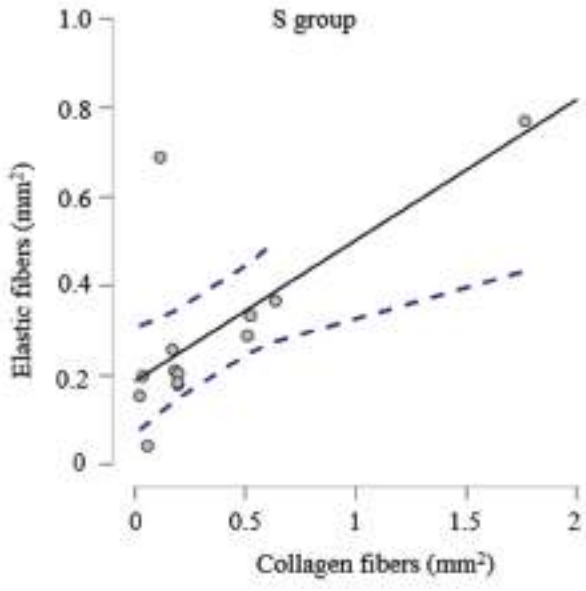
Unlike collagen, the distribution of elastic fibres showed no statistically significant differences between the groups **(Graph 3)**. The mean area occupied by elastic fibres was 0.3 ± 0.15 mm² in the HP group, compared with 0.29 ± 0.21 mm² in the S group (U = 133.000; p = 0.540; rank-biserial correlation = -0.137, 95% CI [-0.505, 0.274]).

The mean elastin content was 20.39% in the HP group and 31.23% in the S group **(Graph 4)**; this difference was not statistically significant (U = 106.000, p = 0.678).

Correlation analysis across the total sample revealed no statistically significant association between the density of collagen and elastic fibres when the two



Graph 4. Elastin-to-lung ratio between groups (U = 106.000, p = 0.678)



Graph 5. Correlation between collagen and elastic fiber density of S group (ρ = 0.632; p = 0.024; effect size [z] = 0.745)

study groups were pooled (ρ = 0.303; p = 0.098; effect size [*z*] = 0.313). In the S group, a statistically significant, strong positive correlation was observed between collagen and elastic fibre density (ρ = 0.632; p = 0.024; effect size [*z*] = 0.745, **Graph 5**). By contrast, no statistically significant correlation was found between collagen and elastic fibre density within the HP group (ρ = -0.108; p = 0.668; effect size [*z*] = -0.109). Within the HP group, there was also no statistically significant difference in collagen area (U = 55.000; p = 0.203) or elastin area (U = 55.000; p = 0.203) between the fibrotic and non-fibrotic forms of the disease. Correlation analysis further showed no statistically significant association between patient age and the density of either collagen (rho = -0.048; p = 0.797) or elastic fibres (rho = 0.140; p = 0.453) across the entire study sample.

Discussion

In the present study, analysis of collagen and elastic fibre distribution revealed a higher density and proportion of collagen fibres in specimens from patients with hypersensitivity pneumonitis than in those with sarcoidosis. Previous studies indicate that collagen fibre deposition and granuloma formation occur in both HP [4,6] and sarcoidosis [9,12], supporting the existence of potential histopathological overlap between the two conditions. Although granulomas in HP are typically smaller, poorly formed, and ill-defined [2,8] - in contrast to sarcoidosis, which predominantly features well-formed granulomas [11,12] - the development of diffuse fibrotic foci interspersed with areas of granulomatous inflammation in HP can mimic the histopathological appearance of sarcoidosis, thereby complicating precise diagnosis. Particularly in such borderline cases, the findings of this study may aid differential diagnosis by demonstrating that HP is characterised by a significantly higher density and proportion of collagen fibres than sarcoidosis. Given the demonstrably higher collagen density and proportion in the specimens analysed, quantitative measurements of the epithelial and interstitial areas suggest that pulmonary parenchymal remodelling is more pronounced in hypersensitivity pneumonitis than in sarcoidosis.

The analysis of elastic fibre distribution, by contrast, found no differences in density or proportion between the two conditions, suggesting that this marker is unlikely to be useful in differential diagnosis. Unlike collagen, the relatively stable distribution of elastic fibres suggests that more pronounced collagen deposition is the principal factor underlying interstitial remodelling. In principle, a more aggressive clinical course, with frequent acute exacerbations of HP, might be expected to cause destruction of elastic fibres and a corresponding reduction in their density; however, the results of this study did not support this, as elastin distribution did not differ from that observed in sarcoidosis. The lower collagen proportion observed in sarcoidosis in this study is consistent with the histological finding of preserved alveolar tissue. Indeed, histological examination of patients with sarcoidosis revealed relative preservation of alveolar tissue, even in areas with granulomas. In the sarcoidosis group, the correlation analysis further indicated that the deposition of connective fibres (collagen and elastic) occurs proportionally. In contrast, in the hypersensitivity pneumonitis group, that process appears asymmetrical, owing to substantially more pronounced collagen deposition. Taken together with previous studies [10,13,14] indicating that fibrosis in sarcoidosis begins at the periphery of the granuloma – reflecting an increased presence of fibroblasts and collagen fibres there - before spreading towards the centre, this specific morphological pattern, together with preservation of the surrounding alveolar tissue, provides clear support to a diagnosis of sarcoidosis and may considerably ease histopathological differentiation.

Analyses of clinical characteristics, including smoking status and occupation, as well as age and sex, revealed no significant differences between the groups.

HP can be divided into two forms: a non-fibrotic, acute/subacute (inflammatory) form, and a chronic (fibrotic) form [6]. Fibrotic HP is characterised by patchy fibrosis with a subpleural and paraseptal dis-

tribution, fibroblastic foci, honeycombing, and diffuse collagen fibrosis; the predominant involvement of the centrilobular and peribronchial regions by fibrosis helps to distinguish HP from other forms of interstitial pneumonia [6]. Although granulomas and multinucleated giant cells occur less frequently in chronic HP, they remain a significant histopathological finding and, unlike in the acute or subacute form, where they are typically located only peribronchially, may occur anywhere within the lung parenchyma [4]. The classification of HP into fibrotic and non-fibrotic forms is based on clinicopathological correlation. It may also reflect different stages in disease progression, particularly as lung biopsies are often obtained during the early phases of the disease. In our cohort, no statistically significant differences were observed in the density or proportion of collagen or elastic fibres between the fibrotic and non-fibrotic HP subgroups. These findings suggest that the inclusion of patients with fibrotic HP did not substantially influence the overall results and that the greater collagen fibre content observed in the HP group, relative to the sarcoidosis group, cannot be attributed solely to the presence of fibrotic HP cases.

In clinical practice, a wide array of diagnostic modalities is available for diagnosing sarcoidosis. Alongside clinical presentation, radiographic imaging, and bronchoalveolar lavage, serum biomarkers are also used, with angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R) levels being the most frequently determined [15]. According to previous studies [15,16], measurement of ACE and sIL-2R levels is not recommended for the initial evaluation or diagnosis of sarcoidosis owing to insufficient sensitivity and specificity.

Given the limitations of serum markers in confirming a diagnosis of sarcoidosis and in cases lacking clear and specific clinical features, the final diagnosis often depends on biopsy findings. In this context, the results of this study may primarily assist in the histopathological differentiation of sarcoidosis from hypersensitivity pneumonitis and, potentially, from other diseases, based on the histopathological characteristics reported here.

A similarly wide range of diagnostic modalities is available for hypersensitivity pneumonitis [16]. These include the determination of specific IgG antibodies reactive to predefined antigens, as well as specific inhalation challenges involving controlled, metered exposure to such antigens, both of which contribute to an accurate diagnosis; however, their clinical use is not routine, and they carry certain limitations [17,18]. Consequently, despite the broad range of diagnostic methods available, including highly specific tests, histopathological evaluation remains essential for assessing and confirming this disease in a subset of cases. Based on the findings of the present study, higher collagen density and proportion can be added to the diagnostic features favouring HP over sarcoidosis in the differential diagnosis and, combined with the future identification of additional biomarkers, may help to differentiate HP and sarcoidosis from other interstitial lung diseases.

Conclusion

Analysis of baseline clinical characteristics, including smoking status, occupation, age, and sex, revealed no statistically significant differences between the study groups. Software-assisted image analysis and statistical evaluation demonstrated higher collagen fibre density and proportion in hypersensitivity pneumonitis specimens than in those from patients with sarcoidosis. In contrast, no significant differences were observed in the density or proportion of elastic fibres between the two conditions. Correlation analysis further showed that collagen and elastic fibre deposition progressed proportionally in sarcoidosis, whereas this relationship was not observed in hypersensitivity pneumonitis.

References

1. Popević S, Bukurović Sudić E, Uskoković Stefanović Ž, Dudvarski Ilić A, Stjepanović MI, Mihailović Vučinić V. Modern bronhoscopic diagnosis of sarcoidosis. Med Pregl. 2013;66(1):17-21.

2. Judson MA. Granulomatous sarcoidosis mimics. Front Med (Lausanne). 2021;8:680989.

3. Bonham CA, Strek ME, Patterson KC. From granuloma to fibrosis: sarcoidosis associated pulmonary fibrosis. Curr Opin Pulm Med. 2016;22(5):484-91.

4. Churg A. Hypersensitivity pneumonitis: new concepts and classifications. Mod Pathol. 2022;35(Suppl 1):15-27.

5. Castonguay MC, Ryu JH, Yi ES, Tazelaar HD. Granulomas and giant cells in hypersensitivity pneumonitis. Hum Pathol. 2015;46(4):607-13.

6. Varone F, Iovene B, Sgalla G, Cavello M, Calabrese A, Larici AR, et al. Fibrotic hypersensitivity pneumonitis: diagnosis and managment. Lung. 2020;198(3):429-40.

7. Coleman A, Colby TV. Histologic diagnosis of extrinsic allergic alveolitis. Am J Surg Pathol. 1988;12(7):514-8.

8. Kawanami O, Basset F, Barrios R, Lacronique JG, Ferrans VJ, Crystal RG. Hypersensitivity pneumonitis in man. Light- and electron-microscopic studies of 18 lung biopsies. Am J Pathol. 1983;110(3):275-89.

9. Patterson KC, Hogarth K, Husain AN, Sperling AI, Niewold TB. The clinical and immunologic features of pulmonary fibrosis in sarcoidosis. Transl Res. 2012;160(5):321-31.

10. Asif H, Ribeiro Neto M, Culver D. Pulmonary fibrosis in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2023;40(3): e2023027.

11. Sakthivel P, Bruder D. Mechanism of granuloma formation in sarcoidosis. Curr Opin Hematol. 2017;24(1):59-65.

12. Broos CE, van Nimwegen M, Hoogsteden HC, Hendriks RW, Kool M, van den Blink B. Granuloma formation in pulmonary sarcoidosis. Front Immunol. 2013;4:437.

13. Zhang C, Chan KM, Schmidt LA, Myers JL. Histopathology of explanted lungs from patients with a diagnosis of pulmonary sarcoidosis. Chest. 2016;149(2):499-507.

14. Tana C, Donatiello I, Caputo A, Tana M, Naccarelli T, Mantini C, et al. Clinical features, histopathology and differential diagnosis of sarcoidosis. Cells. 2021;11(1):59.

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BIBLID.0025-8105:(2026):LXXIX:3-6:109-115.

15. Li Y, Xu G. Diagnostic value of imaging and serological biomarkers in pulmonary sarcoidosis. Adv Respir Med. 2024;92 (3):190-201.

16. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis. An Official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020;201(8):e26-51.

17. Barnes H, Troy L, Lee CT, Sperling A, Strek M, Glaspole I. Hypersensitivity pneumonitis: current concepts in pathogenesis, diagnosis, and treatment. Allergy. 2022;77(2):442-53.

18. Millerick-May ML, Mulks MH, Gerlach J, Flaherty KR, Schmidt SL, Martinez FJ, et al. Hypersensitivity pneumonitis and antigen identification - an alternate approach. Respir Med. 2016;112:97-105.

PREDICTORS OF RECURRENCE OF SUDDEN CARDIAC ARREST IN PATIENTS TREATED WITH AN IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

PREDIKTORI RECIDIVA SRČANOG ZASTOJA KOD PACIJENATA LEČENIH IMPLANTABILNIM KARDIOVERTER DEFIBRILATOROM

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Abstract

Introduction. Randomised clinical trials have demonstrated the indispensable role of implantable cardioverter defibrillators in reducing mortality among patients at high risk of sudden cardiac death. This study aimed to assess the incidence and predictors of cardiac arrest recurrence in such patients. **Material and Methods.** This retrospective study included 240 patients who underwent defibrillator implantation for secondary prevention at the Institute for Cardiovascular Diseases of Vojvodina between 2008 and 2020. The cumulative incidence of recurrence was determined using Kaplan–Meier curves, while Cox regression was used to identify predictors of sudden cardiac arrest recurrence. **Results.** The median follow-up was 4.46 years, and recurrence of sudden cardiac arrest occurred in 60% (n=144) of patients. Sustained ventricular tachycardia as the indication for implantation was shown to be an independent predictor of recurrence. These patients also had a significantly higher number of hospitalisations during follow-up. Patients diagnosed with channelopathy or arrhythmogenic right ventricular dysplasia had a significantly higher number of hospitalisations than those diagnosed with ischaemic or non-ischaemic cardiomyopathy. **Conclusion.** The incidence of sudden cardiac arrest recurrence following defibrillator implantation is high across all patient groups, regardless of aetiology. Sustained ventricular tachycardia as the indication for device implantation predicts a higher incidence of cardiac arrest recurrence.

Key words: Death, Sudden, Cardiac; Defibrillators, Implantable; Risk Factors; Treatment Outcome; Recurrence; Arrhythmias, Cardiac

Sažetak

Uvod. Randomizovane kliničke studije su pokazale nezamenljivu ulogu implantabilnih kardioverter defibrilatora u redukciji mortaliteta pacijenata sa visokim rizikom za iznenadnu srčanu smrt. Cilj istraživanja bio je određivanje incidencije i prediktivnih faktora recidiva iznenadnog srčanog zastoja kod ovih pacijenata. **Materijal i metode.** Sprovedena retrospektivna studija uključila je 240 pacijenata kojima je defibrilator ugrađen u Institutu za kardiovaskularne bolesti Vojvodine u periodu od 2008. do 2020. godine u cilju sekundarne prevencije. Kumulativna incidencija recidiva srčanog zastoja je procenjena korišćenjem Kaplan-Majerovih krivih, dok je Koksova regresija upotrebljena radi procene prediktivnih faktora recidiva iznenadnog srčanog zastoja. **Rezultati.** Medijana perioda praćenja bila je 4,46 godina, dok je 60% pacijenata (n = 144) imalo recidiv iznenadnog srčanog zastoja. Pokazalo se da je postojana ventrikularna tahikardija kao indikacija za ugradnju uređaja bila jedini nezavisan prediktor ponovnog srčanog zastoja. Ovi pacijenti su takođe imali značajno veći broj hospitalizacija tokom perioda praćenja. Pacijenti sa dijagnozom kanalopatije ili aritmogene displazije desne komore su imali značajno češći broj hospitalizacija u poređenju sa pacijentima sa ishemijskom ili neishemijskim kardiomiopatijama. **Zaključak.** Incidencija ponovnog srčanog zastoja nakon ugradnje implantabilnog kardioverter defibrilatora je visoka bez obzira na etiologiju. Postojana ventrikularna tahikardija kao indikacija za implantaciju uređaja predviđa veću incidenciju recidiva srčanog zastoja.

Ključne reči: srčani zastoj; implantabilni kardioverter; faktori rizika; ishod lečenja; recidivi; aritmije

Introduction

Secondary prevention of sudden cardiac death (SCD) aims to reduce the risk of SCD in patients who have survived an episode of sudden cardiac arrest (SCA) or a life-threatening arrhythmia [1]. Most cases of SCA occur in outpatient settings, with over 300,000 out-of-hospital cardiac arrests (OHCA) recorded annually in the United States, where estimated survival is 10%, falling to 6% for OHCA occurring at home [2]. Survival rates vary across European regions [3]. The aetiology of SCA and SCD differs markedly with age. In populations older than 35 years, the most common underlying pathology is coronary artery disease, accounting for approximately 65–80% of SCD cases [1,2,4,5], often as its first and only manifestation [1,2,6]. In those under 35 years, the most common pathologies are genetic structural disorders and cardiomyopathies (e.g. hereditary idiopathic dilated cardiomyopathy [IDC], hypertrophic cardiomyopathy [HCM], or arrhythmogenic right ventricular dysplasia [ARVD]), primary electrical

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Abbreviations

SCD – sudden cardiac death
SCA – sudden cardiac arrest
OHCA – out-of-hospital cardiac arrest
IDC – idiopathic dilated cardiomyopathy
HCM – hypertrophic cardiomyopathy
ARVD – arrhythmogenic right ventricular dysplasia
ICD – implantable cardioverter defibrillator
VF – ventricular fibrillation
VT – ventricular tachycardia
ICD-Tx – implantable cardioverter defibrillator therapy
ATP – anti-tachycardia pacing
LVEF – left ventricular ejection fraction
ICM – ischaemic cardiomyopathy
NICM – non-ischaemic cardiomyopathy
HFrEF – heart failure with reduced left ventricular ejection fraction
HFpEF – heart failure with preserved left ventricular ejection fraction
NIDCM – non-ischaemic dilated cardiomyopathy

disorders (e.g. long QT syndrome or Brugada syndrome), congenital heart disease, myocarditis, and other causes [1,2,5–8].

Implantable cardioverter defibrillators (ICDs) are recommended for secondary prevention of SCD in patients with documented ventricular fibrillation (VF) or haemodynamically unstable ventricular tachycardia (VT) in the absence of reversible causes, provided these arrhythmias did not occur within the first 48 hours of acute myocardial infarction [1]. ICDs continuously monitor the heart's electrical activity and deliver therapies (ICD-Tx), such as anti-tachycardia pacing (ATP) or electrical shock to terminate arrhythmia episodes meeting their pre-programmed parameters [2,9]. Randomised clinical trials have demonstrated the indispensable role of ICDs in reducing mortality among patients at high risk of SCD, regardless of the level of prevention or the underlying heart disease [10–14]. This study aimed to assess the cumulative incidence and predictors of SCA recurrence in patients with an ICD implanted for secondary prevention.

Material and Methods

This retrospective observational study included 240 patients who underwent ICD implantation at the Institute for Cardiovascular Diseases of Vojvodina between 2008 and 2020. In line with European Society of Cardiology guidelines, the inclusion criterion was ICD implantation following a documented episode of VF or haemodynamically unstable VT in the absence of reversible causes or acute myocardial infarction [1].

Data were collected from the hospital information system during 2021–2022 and included demographic features (age and sex); data obtained by ICD interrogation (time to first ICD-Tx, number of ICD-Tx episodes, and SCA recurrences); and clinical features, including left ventricular ejection fraction (LVEF), VF or VT as the index arrhythmia, the arrhythmogenic substrate (ischaemic cardiomyopathy [ICM], non-ischaemic cardiomyopathy [NICM], long QT syndrome, Brugada syndrome, or ARVD), the presence of heart failure with reduced LVEF (HFrEF) or heart failure with preserved LVEF (HFpEF), and the number of hospitalisations due to electrical storm.

Follow-up duration differed significantly between patients with and without SCA recurrence, owing to the wide range of implantation dates. To enable comparison between these groups, patients were further divided into two subgroups according to follow-up duration: 1 to 5 years, and longer than 5 years. Continuous variables are expressed as medians, and categorical variables as percentages. The chi-squared test was used to compare categorical variables, and the Mann–Whitney test to compare numerical variables. Cox regression analysis was used to identify independent predictors of appropriate ICD-Tx. Cumulative incidences of appropriate ICD-Tx, both for all patients and for patients with different arrhythmogenic substrates, were estimated using Kaplan–Meier curves and compared using the log-rank test. The influence of clinical features on time to first ICD-Tx, the absolute number of ICD-Tx episodes, SCA recurrences, and hospitalisations was assessed using the Kruskal–Wallis test, the Mann–Whitney test, and Spearman's rank-order correlation.

Results

During the follow-up period (median 4.46 years), 144 patients (60%) received at least one ICD-Tx. A total of approximately 3,620 ICD-Tx episodes were delivered (range 1–560). Prior sustained VT was the index arrhythmia in 60.5% of cases. Patient characteristics are shown in the first section of **Table 1**.

VT as the index arrhythmia was significantly more frequent (p=0.03) among patients who experienced SCA recurrence, in the analysis comparing subgroups followed up for 1 to 5 years. No statistically significant difference was observed in the presence of ICM, NICM, channelopathies, ARVD, HFrEF, HFpEF, or LVEF between patients with and without SCA recurrence in this subgroup (second section of **Table 1**.

Analysis of patients followed up for longer than 5 years (third section of **Table 1**) likewise showed no statistically significant difference in the presence of ICM, NICM, channelopathies, ARVD, HFrEF, HFpEF, VT as the index arrhythmia, or LVEF between patients with and without SCA recurrence.

Cox regression analysis showed that the only independent predictor of SCA recurrence was prior

Table 1. Basic patient characteristics (section 1); Chi-squared and Mann–Whitney test results (sections 2 and 3)

Demographic and clinical features	Total n=240	SCA recurrence (n=144, 60%)	No SCA recurrence (n=96, 40%)	p-value
Male sex	80.8%	81.3%	80.2%	
Age (years)	63 (20–83)	35 (18–66)	65 (32–81)	
ICM	60.9%	59%	64.6%	
NICM	32.8%	37.5%	31.3%	
Long QT, Brugada, ARVD	4.2%	5.6%	2.1%	
HFrEF	77.3%	75.7%	80.2%	
HFpEF	5%	4.9%	5.2%	
VT – index arrhythmia	60.5%	67.4%	50.5%	
LVEF	35 (18–66)	35 (18–66)	35 (18–65)	
Follow-up 1–5 years	n=126	n=63, 50%	n=63, 50%	
Male sex	83.3%	80.95%	85.71%	0.47
Age (years)	67 (22–81)	67 (22–81)	66.5 (32–81)	0.77
ICM	66.7%	58.7%	74.6%	0.06
NICM	28.6%	34.9%	22.2%	0.11
Long QT, Brugada, ARVD	4.9%	8.1%	1.6%	0.10
HFrEF	81%	74.6%	87.3%	0.07
HFpEF	4%	4.8%	3.2%	0.65
VT – index arrhythmia	61.9%	74.1%	52.4%	0.03
LVEF	35.5 (18–66)	38 (19–66)	34 (18–60)	0.10
Follow-up >5 years	n=99	n=68, 68.7%	n=31, 31.3%	
Male sex	78.8%	83.82%	67.74%	0.07
Age (years)	60 (20–76)	59.5 (20–76)	60 (35–76)	0.43
ICM	54.5%	58.8%	45.2%	0.20
NICM	42.4%	39.7%	48.4%	0.42
Long QT, Brugada, ARVD	4%	4.4%	3.2%	0.78
HFrEF	71.7%	75%	64.5%	0.28
HFpEF	7.1%	5.9%	9.7%	0.49
VT – index arrhythmia	60.6%	64.7%	48.4%	0.12
LVEF	35 (18–65)	35 (19–65)	38 (18–65)	0.63

sustained VT as the index arrhythmia (hazard ratio [HR]: 1.948, 95% confidence interval [CI]: 1.335–2.842, p=0.001). As shown in **Table 2**, these patients also had a significantly higher absolute number of ICD-Tx episodes and life-threatening arrhythmia episodes. **Table 2** further shows that patients diagnosed with channelopathy or ARVD had a significantly higher number of hospitalisations than those diagnosed with ICM or NICM. Time to first ICD-Tx did not differ significantly according to underlying cardiomyopathy, index arrhythmia, LVEF, or the presence or absence of heart failure (**Table 2**).

Cumulative incidences of ICD-Tx for all patients (**Figure 1**) and for patients with different arrhythmogenic substrates (**Figure 2**) were estimated using

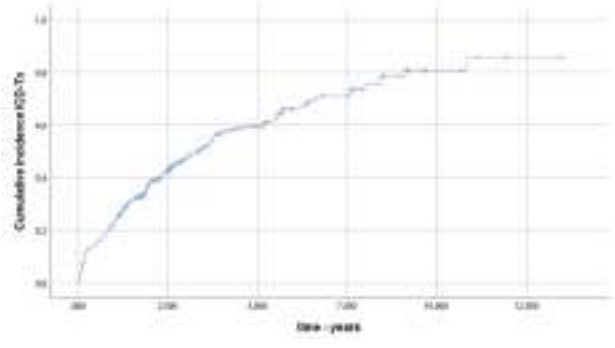

Figure 1. Cumulative incidence of ICD-Tx in all patients

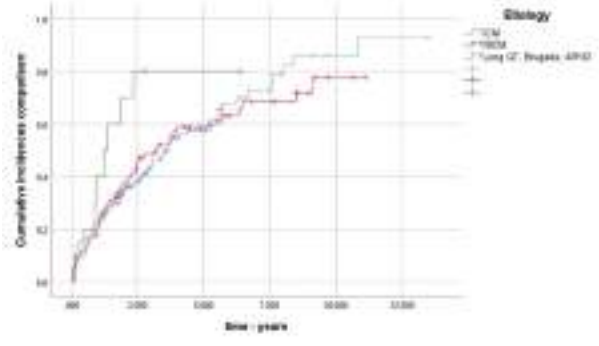

Figure 2. Cumulative incidence of ICD-Tx in patients with different arrhythmogenic substrates

Table 2. Influence of clinical features on number of hospitalisations, ICD-Tx episodes, SCA episodes, and time to first ICD-Tx (Kruskal–Wallis test, Mann–Whitney test, and Spearman's rank-order correlation results)

	Time to first ICD-Tx (months)	p-value	Number of hospitalisations	p-value
ICM	19.53 (0.03–192)	0.337	0 (0–11)	0.043
NICM	18.47 (0.23–109.2)		0 (0–5)	
Long QT, Brugada, ARVD	10.73 (1.3–34.1)		1.5 (0–6)	
HFrEF	18.78 (0.23–192)	0.469	1 (0–2)	0.631
HFpEF	34.53 (0.37–66.4)		0 (0–4)	
No HF	11.57 (0.03–109.2)		0 (0–6)	
VT	17.7 (0.03–101.6)	0.315	0 (0–11)	0.078
VF	21.87 (1–192)		0 (0–6)	
LVEF		0.560		0.476
	Number of ICD-Tx episodes	p-value	Number of SCA episodes	p-value
ICM	6 (1–560)	0.526	5 (1–547)	0.386
NICM	6 (1–150)		5 (1–150)	
Long QT, Brugada, ARVD	10 (2–328)		11 (2–324)	
HFrEF	6 (1–560)	0.725	6 (1–547)	0.607
HFpEF	7 (1–128)		6 (1–125)	
No HF	4 (1–328)		3 (1–324)	
VT	8 (1–560)	0.000	7.5 (1–547)	0.000
VF	3.5 (1–150)		3.5 (1–150)	
LVEF		0.929		0.931

Table 3. Cumulative incidence of SCA recurrence by year of follow-up

Year of follow-up – cumulative incidence (%)	Year 1	Year 2	Year 5	Year 10
All patients	23.2	38.1	59.3	80.7
ICM	22.2	35.6	57.6	85.9
NICM	20	38.2	61	77.5
Long QT, Brugada, ARVD	40	70	80	80
Patients at risk for the period	n=236	n=182	n=63	n=11

Kaplan–Meier curves. The log-rank test showed no statistically significant difference in cumulative incidence of SCA recurrence between patients with ICM, NICM, and ARVD/channelopathies. Cumulative incidences of SCA recurrence are shown in **Table 3**.

Discussion

AVID, CASH, and CIDS are randomised clinical trials that have shown the superiority of ICD implantation for secondary prevention, reducing overall and arrhythmic mortality by 28% and 50% respectively, compared with antiarrhythmic drug therapy alone [12–14]. Borleffs et al. studied 456 patients with an ICD implanted for secondary prevention of SCD in a prospective study with a mean follow-up of 4.5 years, reporting five-year and ten-year cumulative incidences of ICD-Tx of 52% and 61% respectively [15]; similar results were obtained in the retrospective study by Schaer et al., which included 357 patients with a mean follow-up of 6.83 years and five-year and ten-year cumulative incidences of 59.2% and 65.3% [16]. The five-year cumulative incidence of 59.3% in our study was comparable to the findings reported by others. In contrast, our ten-year cumulative incidence was higher at 80.7%, possibly reflecting the smaller number of patients followed beyond 10 years. Lower values were reported in a retrospective Japanese study, in which Nagahara et al. found one-year, three-year, and five-year ICD-Tx rates of 32%, 49%, and 46% respectively [17]. Takano et al. conducted a prospective study with a mean follow-up of 2.4 years, including 96 patients with ICM, in which one-year, three-year, and five-year cumulative incidences of ICD-Tx were 26%, 53.1%, and 64.6% respectively [18] – similar to our patients with ICM, in whom the corresponding values were 22.2%, 47%, and 57.6%.

Schaer et al. identified age (HR: 1.024, 95% CI: 1.010–1.038, p=0.001) and VT as the presenting arrhythmia (HR: 1.450, 95% CI: 1.047–2.008, p=0.025) as independent predictors of SCA recurrence [16]. Borleffs et al. identified atrial fibrillation or flutter, VT presentation (HR: 1.51, 95% CI: 1.05–2.18), a

wider QRS complex, and lower LVEF as independent predictors, with atrial fibrillation the strongest predictor (HR: 2.1, 95% CI: 1.3–3.2) [15]. In a prospective study restricted to patients with ICM, Takano et al. identified higher creatinine levels (HR: 1.294, 95% CI: 1.020–1.641, p=0.034), lower LVEF (HR: 3.713, 95% CI: 1.920–7.180, p<0.001), and incomplete revascularisation (HR: 2.406, 95% CI: 1.179–4.910, p=0.016) as independent predictors of appropriate ICD-Tx [18]. Nagahara et al. found that persistent VT as the cause of implantation was the only independent predictor of SCA recurrence (HR: 2.80, 95% CI: 1.60–4.46, p=0.001) [17], consistent with our findings (HR: 1.948, 95% CI: 1.335–2.842, p=0.001). A comparable result was obtained in the AVID randomised clinical trial in 1997, in which Klein et al. found a significantly higher cumulative incidence of ICD-Tx in patients whose ICD was implanted following an episode of VT (p=0.001) than in those whose index arrhythmia was VF [14]. It remains unclear why recurrence rates differ according to index arrhythmia; one possible explanation is the stability of the reentry circuit substrate characteristic of monomorphic VT, which allows greater reproducibility of ventricular arrhythmias of sufficient duration to trigger appropriate ICD-Tx [17].

Whether the risk of SCA recurrence varies with the underlying aetiology of ventricular arrhythmia also remains unclear. Nagahara et al.'s study included 50 patients with ICM, 15 with non-ischaemic dilated cardiomyopathy (NIDCM), 33 with HCM, 10 with ARVD, 16 with cardiac sarcoidosis, and 11 with valvular heart disease. They found no significant difference in aetiology between patients with and without SCA recurrence [17]. Dharma et al. compared the incidence of appropriate ICD-Tx between patients with ICM and NICM in a study in which 26% of patients had an ICD implanted for secondary prevention, finding comparable incidences over a mean follow-up of 19 months [19]. Our results are consistent with these studies, with no significant difference observed in the cumulative incidence of SCA recurrence across different arrhythmia aetiologies.

These findings support the utility of ICDs in preventing SCD, regardless of quality-of-life considerations or long-term patient acceptance of the device [20,21].

Conclusion

The incidence of implantable cardioverter defibrillator therapy delivery is high among patients treated for secondary prevention of sudden cardiac death, regardless of aetiology. Prior sustained ventricular tachycardia as the indication for implantable cardioverter defibrillator implantation predicted a higher incidence and absolute number of appropriate defibrillator therapies. Various studies have sought to identify predictors of sudden cardiac arrest recurrence following defibrillator implantation for secondary prevention of sudden cardiac death; however, no reliable predictor has yet been identified.

References

1. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022;43(40):3997-4126.

2. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Circulation. 2018;138(13): e272-391.

3. Oving I, de Graaf C, Masterson S, Koster RW, Zwinderman AH, Stieglis R, et al. European first responder systems and differences in return of spontaneous circulation and survival after out-of-hospital cardiac arrest: a study of registry cohorts. Lancet Reg Health Eur. 2020;1:100004.

4. Spain DM, Bradess VA, Mohr C. Coronary atherosclerosis as a cause of unexpected and unexplained death. An autopsy study from 1949-1959. JAMA. 1960;174(4):384-8.

5. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. Circ Res. 2015; 116(12):1887-906.

6. Tomaselli GF, Zipes DP. Approach to the patient with cardiac arrhythmias. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Braunwald E, editors. Braunwald's heart disease. 11th ed. Philadelphia: Elsevier; 2018. p. 597-603.

7. Kaltman JR, Thompson PD, Lantos J, Berul CI, Botkin J, Cohen JT, et al. Screening for sudden cardiac death in the young: report from a National Heart, Lung, and Blood Institute Working group. Circulation. 2011;123(17):1911-8.

8. Puranik R, Chow CK, Duflou JA, Kilborn MJ, McGuire MA. Sudden death in the young. Heart Rhythm. 2005;2(12):1277-82.

9. Aguiar Rosa S, Silva Cunha P, Lousinha A, Valente B, Delgado AS, Pimenta R, et al. Importance of monitoring zones in the detection of arrhythmias in patients with implantable cardioverter-defibrillators under remote monitoring. Rev Port Cardiol (Engl Ed). 2019;38(1):11-6.

10. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002; 346(12):877-83.

11. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004;350(21):2151-8.

12. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable defibrillator against amiodarone. Circulation. 2000;101(11):1297-302.

13. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibril-

lators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation. 2000;102(7):748-54.

14. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmia. N Engl J Med. 1997;337 (22):1576-84.

15. Borleffs CJ, van Erven L, Schotman M, Boersma E, Kies P, van der Burg AE, et al. Recurrence of ventricular arrhythmias in ischaemic secondary prevention implantable cardioverter defibrillator recipients: long-term follow-up of the Leiden out-of-hospital cardiac arrest study (LOHCAT). Eur Heart J. 2009;30(13):1621-6.

16. Schaer B, Kühne M, Reichlin T, Osswald S, Sticherling C. Incidence of and predictors for appropriate implantable cardioverter-defibrillator therapy in patients with a secondary preventive implantable cardioverter-defibrillator indication. Europace. 2016;18(2):227-31.

17. Nagahara D, Fujito T, Mochizuki A, Shimoshige S, Hashimoto A, Miura T. Predictors of appropriate ICD therapy in Japanese patients with structural heart diseases: a major role of prior sustained ventricular tachycardia in secondary prevention. J Arrhythm. 2018;34(5):527-35.

18. Takano T, Tanaka K, Ozaki K, Sato A, Iijima K, Yanagawa T, et al. Clinical predictors of recurrent ventricular arrhythmias in secondary prevention implantable cardioverter defibrillator recipients with coronary artery disease - lower left ventricular ejection fraction and incomplete revascularization. Circ J. 2018; 82(12):3037-43.

19. Darma A, Nedios S, Kosiuk J, Richter S, Doering M, Arya A, et al. Differences in predictors of implantable cardioverter-defibrillator therapies in patients with ischaemic and non-ischaemic cardiomyopathies. Europace. 2016;18(3):405-12.

20. Ristić A, Brusnjai V, Ađić M, Dević M, Aleksandrić T, Ađić F. Quality of life of patients with pacemakers. Med Pregl. 2025;78(5-8):167-72.

21. Januszkiewicz Ł, Barra S, Providencia R, Conte G, de Asmundis C, Chun JKR, et al. Long-term quality of life and acceptance of implantable cardioverter-defibrillator therapy: results of the European Heart Rhythm Association survey. Europace. 2022;24(5):860-7.

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MORPHOMETRIC ANALYSIS OF THE HAND IN YOUNG ADULTS

MORFOMETRIJSKA ANALIZA ŠAKE OSOBA MLAĐE ŽIVOTNE DOBI

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Abstract

Introduction. The hand is the distal part of the upper limb and has a complex structure that enables a high degree of mobility and grasping. Hand morphometric characteristics exhibit sexual dimorphism, as well as ethnic and racial variations. Contemporary studies indicate that hand morphology changes throughout ontogenesis, with sex differences becoming fully expressed in adulthood. This study aimed to conduct a morphometric analysis of the hand in young adults and determine differences by body side and sex. **Material and Methods.** The study included 140 participants of both sexes, with a mean age of 19.83±0.98 years. The anthropometric parameters analysed included hand widths (S1–S3), palm lengths (D1–D5), and finger lengths (P1–P5). **Results.** In both sexes, thumb length (P1) was significantly greater on the right hand. In females, parameters S1 and S3 were significantly higher on the right hand, whilst D4 and D5 were higher on the left. In males, D3, D4, D5, and P5 were significantly greater on the left hand, whereas S2 was higher on the right. Comparison between sexes revealed statistically significant differences across all measured parameters, with males consistently exhibiting higher values. **Conclusion.** Significant sex-related differences in hand morphometric parameters were observed, with males showing higher values across nearly all measured dimensions. Bilateral asymmetry was present in both sexes.

Key words: Anthropometry; Anatomy, Regional; Hand; Upper Extremity; Young Adult; Sex Factors; Functional Laterality

Sažetak

Uvod. Šaka predstavlja distalni deo gornjeg ekstremiteta i odlikuje se složenom građom koja omogućava visok stepen pokretljivosti i funkciju hvata. Morfometrijske karakteristike šake pokazuju polni dimorfizam, kao i etničke i rasne razlike. Savremena istraživanja ukazuju da se morfologija šake menja tokom ontogeneze, pri čemu polne razlike postaju potpuno izražene u odraslom dobu. Cilj ovog istraživanja bio je da se izvrši morfometrijska analiza šake kod odraslih osoba i utvrde razlike u odnosu na telesnu stranu i pol. **Materijal i metode.** Istraživanjem je obuhvaćeno 140 ispitanika oba pola, prosečne starosti 19,83 ± 0,98 godina. Analizirani su antropometrijski parametri šake: širine šake (S1–S3), dužine dlana (D1–D5) i dužine prstiju (P1–P5). **Rezultati.** Kod oba pola, dužina palca (P1) pokazala je statistički značajno veće vrednosti na desnoj šaci. Kod ispitanica su parametri S1 i S3 bili značajno veći na desnoj šaci, dok su D4 i D5 bili izraženiji na levoj. Kod ispitanika su D3, D4, D5 i P5 imali značajno veće vrednosti na levoj šaci, dok je S2 bio veći na desnoj. Poređenje između polova pokazalo je statistički značajne razlike u svim merenim parametrima, pri čemu su muškarci imali veće vrednosti. **Zaključak.** Utvrđene su značajne polne razlike u morfometrijskim parametrima šake, pri čemu su muškarci pokazali veće vrednosti u gotovo svim dimenzijama. Bilateralna asimetrija uočena je kod ispitanika oba pola.

Ključne reči: antropometrija; regionalna anatomija; ruka; gornji ekstremitet; mladi ljudi; polne razlike; funkcionalna asimetrija

Introduction

The hand is the distal part of the free portion of the upper limb [1]. It consists of 27 bones, arranged into three groups: the carpal bones, the metacarpal bones, and the bones of the fingers [1,2]. These bones are interconnected by 15 joints, whose complex and fine movements are enabled by the flexor and extensor muscles of the fingers, together with 19 intrinsic muscles of the hand [2,3]. From a topographical perspective, the hand is divided into the root of the hand or carpus, the metacarpus, and the fingers [1]. Anatomically, the hand can be described as having anterior and posterior surfaces [2]. The palm and the dorsum of the hand refer, more specifically, to the anterior and posterior parts of the metacarpal region [1,2].

The complex anatomy of the hand - a combination of mobile joints, muscles, and tendons - enables various forms of grip and grasp, which are essential for work efficiency [4–6]. Ergonomics and tool design are often based on the dimensions and functional capacities of the hand to increase productivity and reduce the risk of injury [7,8]. The hand therefore functions not only as an anatomical part of the body but also as a primary tool in interacting with the environment and performing work-related tasks [5,9].

Contemporary research confirms that hand morphology and its parameters change throughout on-

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togenesis, with growth patterns and shaping differing between sexes. Sexual dimorphism becoming more pronounced during development and ultimately fully expressed in adulthood [6,9]. The process of morphological growth and development of the hand is completed between 18 and 25 years of age, and after that period pathological or degenerative changes may occur. Physiological age-related changes of the hand are primarily characterized by gradual alterations in hand size and proportions, while in later stages of life a slight decrease in muscle mass and functional parameterscapacity is observed, without necessarily being accompanied by pronounced morphometric changes in the bones [10]. The functional aspects of the hand also exhibit age-related changes, as ageing is associated with a physiological decline in handgrip strength, which is more pronounced in men [11].

Differences between the right and left hands are manifested as functional and morphological lateralisation, with the dominant hand often exhibiting greater dimensions and strength. This is associated with use and mechanical loading, although these differences are usually small and vary across populations [12]. Sexual dimorphism of the hand is well documented, reflected in the fact that men, on average, have larger absolute hand dimensions - length, palm width, and finger length - than women [8]. These differences are statistically significant, and recent studies have confirmed the ratio of the lengths of the second and fourth digits (2D:4D) as a stable indicator of sexual dimorphism, with women tending to show higher values of this ratio than men, an association attributed to prenatal hormonal influences [12].

In ergonomics, the key dimensions of the hand include hand length, palm width, finger lengths, and finger span. These dimensions have significant applications in ergonomics and biomedical design, as they directly influence the design of tools, prostheses, and the working environment [7].

Previous anthropometric studies indicate that average hand dimensions vary according to sex and population. Adult men most commonly have a hand length of approximately 18–20 cm, whilst in women the range is 16–18 cm, with proportionally smaller palm widths and finger lengths [13–15]. Contemporary studies confirm that hand length, palm width, and finger length are among the most stable and reproducible anthropometric parameters, with relatively low intraindividual variability in adulthood [6,16]. Population differences can also be substantial, indicating the need for regional reference values in anthropometric and ergonomic analyses [13,14,16]. Combining multiple linear hand measurements enables a more accurate assessment of body characteristics and has wide application in forensic anthropology and biomedical engineering [15,16].

Previous morphometric analyses indicate that ethnic differences in hand dimensions and proportions also exist. Populations of European ancestry generally exhibit larger absolute hand dimensions; Asian populations tend to have shorter, relatively wider hands; and African populations tend to have relatively longer fingers in relation to palm length. Although these differences are statistically significant, they overlap across populations and are influenced by factors such as sex, height, and environmental adaptation, and therefore cannot be used as discriminatory criteria [6,16–19].

This study aimed to perform a morphometric analysis of the hand in young adults to determine bilateral (right-left) and sex-related differences in hand dimensions.

Material and Methods

The study was conducted on 140 participants (48 males and 92 females), all first-year students at the Faculty of Medicine, University of Novi Sad, mean age for men below is stated as 19.93±1.03. Inclusion criteria required that participants had no congenital hand malformations, visible deformities, or signs of pathological processes, and no self-reported history of hand injury or previous surgical intervention in the hand region.

The study was carried out at the Department of Anatomy, Faculty of Medicine, University of Novi Sad, following approval from the Faculty of Medicine Ethics Committee (01-39/138/1). All participants provided written informed consent following a detailed briefing about the study.

Photography of the palmar surfaces of both hands was obtained using a Nikon D3400 camera (24 MP), positioned 40 cm from the centre of the palmar surface of the photographed hand, in a room with constant artificial lighting; a single investigator took all photographs. Participants were seated, with the elbow placed close to the trunk and the forearm flexed at 90° relative to the upper arm. The hands were placed in a supinated position, with the fingers maximally abducted, on a table in front of them. A ruler was placed next to each hand and subsequently used for calibration. The digital images were processed using ImageJ 1.48v software, following calibration based on the ruler included in each image. A single investigator performed all measurements.

Statistical analysis was performed using IBM SPSS Statistics v.24. Data distribution was assessed using the Shapiro–Wilk test. Owing to non-normality, continuous variables are presented as median and interquartile range (IQR; 25th–75th percentile), along with

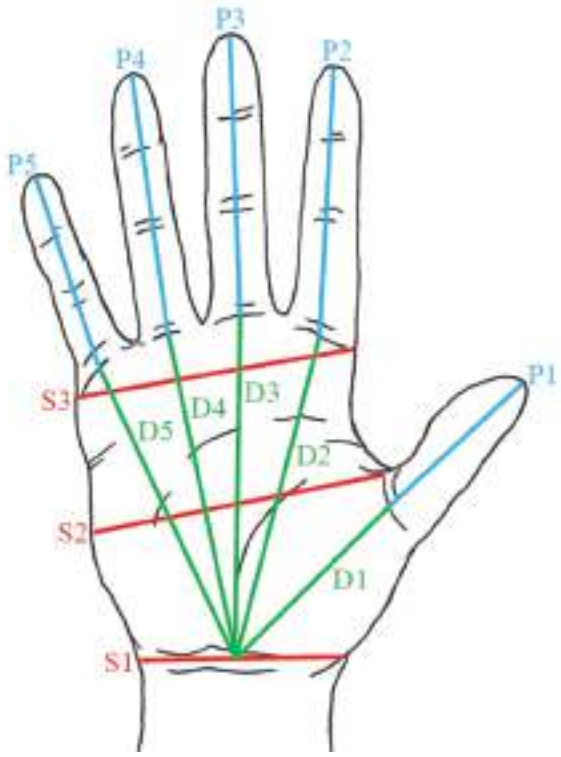

Figure 1. Morphometric parameters of the hand

minimum and maximum values. Differences between the right and left hands within the same group were analysed using the Wilcoxon signed-rank test. Comparisons between male and female participants were performed using the Mann–Whitney U test. A p-value < 0.05 was considered statistically significant.

During measurement, the distal (lower) wrist crease was used as the main anatomical landmark. After measuring the length of this crease, its midpoint was determined and used as the reference point for all other parameters.

The following parameters were measured **(Figure 1):**

– S1 – hand width at the level of the distal wrist crease;

– S2 – hand width from the medial edge of the proximal crease at the base of the thumb to the midpoint of the medial palmar border;

– S3 – hand width from the lateral edge of the proximal crease at the base of the index finger to the medial edge of the proximal crease at the base of the little finger;

– D1 – palm length from the midpoint of the distal wrist crease to the midpoint of the proximal crease at the base of the thumb;

– D2 – palm length from the midpoint of the distal wrist crease to the midpoint of the proximal crease at the base of the index finger;

– D3 – palm length from the midpoint of the distal wrist crease to the midpoint of the proximal crease at the base of the middle finger;

– D4 – palm length from the midpoint of the distal wrist crease to the midpoint of the proximal crease at the base of the ring finger;

– D5 – palm length from the midpoint of the distal wrist crease to the midpoint of the proximal crease at the base of the little finger;

– P1 – thumb length, measured from the midpoint of the proximal thumb crease to the most distal tip of the thumb;

– P2 – index finger length, measured from the midpoint of the proximal index finger crease to the most distal tip of the index finger;

– P3 – middle finger length, measured from the midpoint of the proximal middle finger crease to the most distal tip of the middle finger;

– P4 – ring finger length, measured from the midpoint of the proximal ring finger crease to the most distal tip of the ring finger;

– P5 – little finger length, measured from the midpoint of the proximal little finger crease to the most distal tip of the little finger.

Results

The study included 140 participants, of whom 92 (65.7%) were female, and 48 (34.3%) were male. The mean age of the participants was 19.83±0.98 years (males: 19.93±1.03; females: 19.72±0.9) considering that the number of women in relation to men is higher than in the population.

Table 1 presents all 13 measured anthropometric parameters in female participants, along with differences between the right and left hand.

In female participants, bilateral asymmetry between the right and left hand was observed, with statistically significant differences detected in some parameters. Right-hand dominance was found for S1 ($p = 0.011$), S3 ($p < 0.001$), and P1 ($p < 0.001$), whereas left-hand dominance was found for D4 ($p < 0.001$) and D5 ($p < 0.001$). Most remaining parameters showed no statistically significant difference between sides ($p > 0.05$), indicating that lateralisation was not equally present across all measurements.

Table 2 presents all 13 measured anthropometric parameters of male participants, along with differences between the right and left hand.

In male participants, bilateral asymmetry between the right and left hand was also observed. Statistically significant right-sided dominance was found for S2 ($p = 0.002$) and P1 ($p = 0.001$), whereas left-sided dominance was observed for D3 ($p = 0.022$), D4 ($p =$

Table 1. Morphometric parameters of the right and left hand in femal

	Right hand		Left hand		IQR (mm)		Z	p	Direction
	Min-Max (mm)	Median (mm)	Min-Max (mm)	Median (mm)	R	L			
S1	55.06-77.03	64.25	53.31-75.63	63.65	62.01 - 67.69	61.02 - 68.10	-2.53	**0.011***	R > L
S2	68.51-105.03	88.69	56.14-109.96	85.93	82.04 - 91.42	81.40 - 92.13	-1.79	0.073	/
S3	63.07-102.93	89.41	65.25-105.51	87.98	84.85 - 94.52	82.60 - 93.46	-3.39	**<0.001***	R > L
D1	55.26-113.47	73.66	55.11-114.85	73.51	67.01 - 76.19	68.09 - 77.91	0.89	0.373	/
D2	65.83-124.30	109.99	94.25-126.75	110.18	104.83 - 114.34	105.42 - 115.56	0.16	0.867	/
D3	54.89-131.02	108.67	95.13-130.98	109.12	103.74 - 113.46	105.70 - 115.63	1.90	0.057	/
D4	87.96-125.61	103.52	90.65-125.08	104.28	99.01 - 107.03	101.41 - 110.33	3.42	**<0.001***	L > R
D5	76.32-121.13	93.39	65.76-111.06	95.82	89.75 - 97.77	90.84 - 101.33	3.49	**<0.001***	L > R
P1	48.33-77.74	61.08	39.68-88.67	59.66	56.55 - 64.97	54.81 - 64.20	-3.37	**<0.001***	R > L
P2	59.44-85.27	70.14	56.25-84.95	70.11	67.27 - 73.44	66.83 - 73.21	-1.29	0.196	/
P3	63.39-92.91	76.91	72.41-88.62	77.05	73.96 - 80.17	73.24 - 79.99	1.66	0.971	/
P4	58.84-88.63	71.98	58.42-85.07	71.13	67.08 - 74.90	67.57 - 74.32	-1.09	0.275	/
P5	44.31-72.61	55.48	45.56-74.59	56.11	53.15 - 58.40	53.63 - 59.63	1.40	0.168	/

R – right hand; L – left hand; IQR - interquartile range (25th - 75th percentile); Z - standardised test statistic; *$p < 0.05$ considered statistically significant; R > L – right hand value was significantly higher than left; L > R – left hand value was significantly higher than right

Table 2. Morphometric parameters of the right and left hand in mal

	Right hand		Left hand		IQR (mm)		Z	p	Direction
	Min-Max (mm)	Median (mm)	Min-Max (mm)	Median (mm)	R	L			
S1	61.19-77.95	71.65	63.48-82.82	71.26	68.26-74.26	67.66-73.76	-1.03	0.305	/
S2	86.96-121.94	99.59	82.15-120.25	96.41	93.60-105.96	92.71-105.15	-3.09	**0.002***	R > L
S3	81.25-115.51	97.80	72.72-114.94	97.30	94.29-103.59	93.24-102.92	-1.85	0.065	/
D1	63.33-98.73	78.85	67.85-97.98	79.66	75.71-83.42	76.45-85.17	0.75	0.454	/
D2	105.33-147.95	119.66	108.02-148.49	119.55	114.39-126.50	117.08-124.81	1.48	0.138	/
D3	103.55-148.95	121.88	109.65-146.92	122.89	114.11-127.53	118.52-126.89	2.30	**0.022***	L > R
D4	96.11-142.01	115.10	105.45-144.86	117.57	110.34-123.83	113.74-124.04	2.82	**0.005***	L > R
D5	86.17-133.87	105.33	95.62-133.88	109.13	100.12-114.95	102.92-113.11	2.13	**0.034***	L > R
P1	54.04-88.99	66.55	43.15-88.61	64.32	62.02-73.21	55.71-70.85	-4.27	**< 0.001***	R > L
P2	66.16-96.75	76.25	66.97-93.84	75.66	73.32-79.96	71.81-79.97	0.91	0.360	/
P3	74.18-100.01	82.30	74.36-100.09	81.99	79.40-87.85	79.58-89.31	1.20	0.230	/
P4	67.12-94.99	76.58	68.95-93.77	77.37	74.25-82.16	74.01-83.09	-0.38	0.704	/
P5	49.91-78.25	63.20	54.02-76.89	63.08	59.78-69.09	61.83-70.02	2.69	**0.007***	L > R

R – right hand; L – left hand; IQR - interquartile range (25th - 75th percentile); Z - standardised test statistic; *p < 0.05 considered statistically significant; R > L – right hand value was significantly higher than left; L > R – left hand value was significantly higher than right

0.005), D5 (p = 0.034) and P5 (p = 0.007). The remaining parameters showed no statistically significant differences between sides (p > 0.05) **(Table 2)**. Overall, these findings suggest that hand asymmetry does not follow a uniform pattern across all parameters, although it is present across different segments.

A comparison between male and female participants revealed statistically significant differences in all measured morphometric parameters of both the right and left hand. In general, male participants had consistently higher values across all segments than females (p < 0.001 for most parameters). The only exception was P1L, where the difference, although still statistically significant (p = 0.015), was slightly less pronounced **(Table 3).**

Discussion

The results of this study indicate bilateral hand asymmetry in both sexes, as well as morphometric differences between males and females in segmental hand parameters. In both sexes, thumb length (P1) was greater on the right hand, suggesting a possible influence of functional dominance. In female participants,

Table 3. Comparison of morphometric hand measurements between males and females (Mann–Whitney U test

Parameters	Males Median (IQR) (mm)	Females Median (IQR) (mm)	U	p
S1R	71.65 (68.26 - 74.26)	64.25 (62.01 - 67.69)	712.5	< **0.001***
S2R	99.59 (93.60 - 105.96)	88.69 (82.04 - 91.42)	397.0	< **0.001***
S3R	97.80 (94.29 - 103.59)	89.41 (84.85 - 94.52)	802.5	< **0.001***
D1R	78.85 (75.71 - 83.42)	73.66 (67.01 - 76.19)	967.5	< **0.001***
D2R	119.66 (114.39 - 126.50)	109.99 (104.83 - 114.34)	776.0	< **0.001***
D3R	121.88 (114.11 - 127.53)	108.67 (103.74 - 113.46)	646.0	< **0.001***
D4R	115.10 (110.34 - 123.83)	103.52 (99.01 - 107.03)	686.5	< **0.001***
D5R	105.33 (100.12 - 114.95)	93.39 (89.75 - 97.77)	609.5	< **0.001***
P1R	66.55 (62.02 - 73.21)	61.08 (56.55 - 64.97)	1169.0	< **0.001***
P2R	76.25 (73.32 - 79.96)	70.14 (67.27 - 73.44)	870.0	< **0.001***
P3R	82.30 (79.40 - 87.85)	76.91 (73.96 - 80.17)	740.5	< **0.001***
P4R	76.58 (74.25 - 82.16)	71.98 (67.08 - 74.90)	812.0	< **0.001***
P5R	63.20 (59.78 - 69.09)	55.48 (53.15 - 58.40)	687.5	< **0.001***
S1L	71.26 (67.66 - 73.76)	63.65 (61.02 - 68.10)	748.5	< **0.001***
S2L	96.41 (92.71 - 105.15)	85.93 (81.40 - 92.13)	559.5	< **0.001***
S3L	97.30 (93.24 - 102.92)	87.97 (82.60 - 93.46)	823.5	< **0.001***
D1L	79.66 (76.45 - 85.17)	73.51 (68.09 - 77.91)	901.0	< **0.001***
D2L	119.55 (117.08 - 124.81)	110.18 (105.42 - 115.56)	616.0	< **0.001***
D3L	122.89 (118.52 - 126.89)	109.12 (105.70 - 115.63)	428.0	< **0.001***
D4L	117.57 (113.74 - 124.04)	104.28 (101.41 - 110.33)	434.0	< **0.001***
D5L	109.13 (102.92 - 113.11)	95.82 (90.84 - 101.33)	518.0	< **0.001***
P1L	64.32 (55.71 - 70.85)	59.66 (54.81 - 64.20)	1652.0	**0.015***
P2L	75.66 (71.81 - 79.97)	70.11 (66.83 - 73.21)	959.5	< **0.001***
P3L	81.99 (79.58 - 89.31)	77.05 (73.24 - 79.99)	798.5	< **0.001***
P4L	77.37 (74.01 - 83.09)	71.13 (67.57 - 74.32)	739.0	< **0.001***
P5L	63.08 (61.83 - 70.02)	56.11 (53.63 - 59.63)	526.0	< **0.001***

IQR-interquartile range (25^{th} - 75^{th} percentile); U – value of Mann-Whitney test; * $p < 0.05$ considered statistically significant

higher values on the right hand were also observed for S1 and S3, whereas D4 and D5 were more pronounced on the left hand. In male participants, higher values were observed in the left hand for D3, D4, D5, and P5, whilst S2 was more prominent on the right hand.

Unlike some studies that report more consistent dominance of one side [8,9], the present findings indicate that asymmetry is parameter-specific and does not follow a clear directional pattern. This may reflect individual variability in hand use, as well as differences in daily activities and motor habits among participants. The influence of differing morphometric techniques across studies should also be considered, along with the impact of racial and ethnic differences among the populations studied. Additionally, the relatively young age of the study population may suggest that cumulative functional adaptations are still developing, which could contribute to the absence of a uniform asymmetry pattern.

These findings are consistent with Agnihotri et al. [5], who reported greater overall hand width - measured as the distance between the most lateral point on the head of the second metacarpal and the most medial point on the head of the fifth metacarpal - in males (right hand: 18.89 ± 0.88 cm; left hand: 18.90 ± 0.87 cm) than in females (right and left hand: 17.22 ± 0.92 cm), confirming marked sexual dimorphism. Although that study did not report significant differences between the left and right hand, the present study demonstrates more pronounced bilateral asymmetry, owing to its analysis of segmental parameters (D1–D5, P1–P5), which may be more sensitive to functional in-

fluences and patterns of hand use. It should be noted that hand dominance was not assessed in this study.

Similarly, a study conducted in Egypt [16] demonstrated that all hand dimensions were significantly larger in males, particularly hand breadth - defined as the distance between the heads of the second and fifth metacarpals - which was identified as the best discriminator of sex, with an accuracy of up to 71.8% for the right hand. This finding is consistent with the present study, as width-related parameters (S1, S2, S3) also showed consistent differences between the left and right hands, further confirming sexual dimorphism in these parameters.

Likewise, a study conducted in Nigeria [18] reported that males had significantly greater hand length (18.3 ± 0.6 cm) than females (16.8 ± 0.7 cm), as well as greater hand width (7.5 vs 6.3 cm; $p < 0.001$), together with marked sexual dimorphism in the hand index. In that study, hand width was defined as the distance between the most lateral point of the second metacarpal head and the most medial point of the fifth metacarpal head. These findings are consistent with the present study, in which males exhibited higher values in segmental finger lengths (P3–P5) and width-related parameters (S1, S2, S3).

In addition to sex-related differences, the present study identified bilateral asymmetry between the right and left hands, though not a uniform pattern across all parameters. Previous studies have shown that the dominant hand generally exhibits greater anthropometric values and functional capacity than the non-dominant hand. Napier [9] emphasised the importance of prehensile activity and hand function in shaping hand morphology, whilst Pheasant and Haslegrave [7] suggested that occupational and habitual activities may contribute to asymmetrical development of the hands. Similar findings were reported by Kanchan and Rastogi [8], and by Żuchowska and Żarów [11].

The present study demonstrated clear sex-related differences in hand morphometry, together with parameter-dependent bilateral asymmetry. Whilst sex-related differences were consistent and pronounced across nearly all measured parameters, patterns of asymmetry between the right and left hand were less uniform. These results further support the applicability of hand anthropometry in fields such as forensic science, ergonomics, and clinical practice. Nevertheless, future research involving larger and more diverse populations, along with functional and behavioural variables, would offer a more comprehensive understanding of the factors influencing hand morphology.

This study has several limitations that should be considered when interpreting the results. First, the research was conducted in a relatively homogeneous population of young adults, limiting the generalisability of the findings to other age groups or populations with different demographic characteristics. Although the sample size was sufficient for basic statistical analysis, it may not be adequate for more detailed stratification or more complex statistical modelling, particularly about inter-individual variability in morphometric parameters. A further limitation is the absence of information on hand dominance and participants' levels of physical activity, both of which may significantly influence patterns of bilateral asymmetry. Functional loading and daily manual activities may contribute to morphological differences between the right and left hands, and their absence represents a potential source of unexplained variability. Finally, the study relied on classical morphometric measurements rather than advanced techniques such as 3D scanning or geometric morphometrics, which could provide a more precise and comprehensive analysis of hand shape and structure.

Conclusion

This study demonstrated significant sex-related differences in hand morphometric parameters, with males consistently exhibiting higher values across nearly all measured dimensions compared with females. Bilateral hand asymmetry was also observed in both sexes; however, it did not follow a uniform pattern across all parameters, suggesting that lateralisation is segment-specific rather than consistently directional.

The findings confirm the presence of clear sexual dimorphism in hand dimensions, alongside evidence of asymmetry.

Given the limitations of the study, future research involving larger, more heterogeneous populations, along with additional functional and behavioural variables, is needed to provide a more comprehensive understanding of hand morphological variability.

References

1. Standring S, Gray H, Anand N, Tunstall R, editors. Gray's anatomy: the anatomical basis of clinical practice. 42nd ed. Amsterdam: Elsevier; 2021.

2. Moore KL, Dalley AF, Agur AMR. Clinically oriented anatomy. 8th ed. Philadelphia: Wolters Kluwer; 2019.

3. Drake RL, Vogl AW, Mitchell AWM. Gray's anatomy for students. 4th ed. Philadelphia: Elsevier; 2020.

4. Kücken M, Newell AC. Fingerprint formation. J Theor Biol. 2005;235(1):71-83.

5. Agnihotri AK, Purwar B, Jeebun N, Agnihotri S. Determination of sex by hand dimensions. The Internet Journal of Forensic Science. 2007;1(2):12-24.

6. Fernández-Navarro V, Garate D, Martínez DG. Ontogeny and sexual dimorphism in the human hands through a 2D geo-

metric morphometrics approach. Am J Biol Anthropol. 2024; 185(1):e25001.

7. Pheasant S, Haslegrave CM. Bodyspace: anthropometry, ergonomics and the design of work. 3rd ed. Boca Raton: Taylor and Francis; 2006.

8. Kanchan T, Rastogi P. Sex determination from hand dimensions of north and south Indians. J Forensic Sci. 2009;54(3): 546-50.

9. Napier JR. The prehensile movements of the human hand. J Bone Joint Surg Br. 1956;38-B (4):902-13.

10. Logue Cook RN, Brown SH. Age-related changes in hand function – it's not just about muscle strength. Front Hum Neurosci. 2026;20:1779077.

11. Żuchowska K, Żarów R. Dynamics of changes and sexual dimorphism in dynamometric strength of the stronger hand based on Cracow longitudinal growth study. Health Promotion and Physical Activity. 2025;32(3):1-8.

12. Jägetoft Z, Unenge Hallerbäck M, Julin M, Bornehag CG, Wikström S. Anthropometric measures do not explain the 2D:4D ratio sexual dimorphism in 7-year-old children. Am J Hum Biol. 2022;34(9):e23776.

13. Habib SR, Kamal NN. Stature estimation from hand and phalanges lengths of Egyptians. J Forensic Leg Med. 2010;17(3): 156-60.

14. Rastogi P, Nagesh KR, Yoganarasimha K. Estimation of stature from hand dimensions of north and south Indians. Leg Med (Tokyo). 2008;10(4):185-9.

15. Ibrahim MAB, Khalifa AM, Hagras AM, Alwakid NI. Sex determination from hand dimensions and index/ring finger length ratio North Saudi population: medico-legal view. Egypt J Forensic Sci. 2016;6(4):435-44.

16. Suleiman MO, Danborno B, Musa SA, Timbuak JA, Yusuf AO, Suleiman HO. Sex estimation and sexual dimorphism analysis through hand anthropometry: insights from a cross-sectional study. Forensic Sci Int Rep. 2024;10:100374.

17. Fernández Navarro V, Godinho RM, García Martínez D, Garate Maidagan D. Exploring the utility of Geometric Morphometrics to analyse prehistoric hand stencils. Sci Rep. 2024;14:6336.

18. Şan F, Yaşar ZF, Zengin HY, Bandur İNK, Şekerci D, Şençelikel T. Sex determination from hand dimensions: preliminary study. Turkish Journal of Forensic Medicine. 2024;38(2):114-23.

19. Gazziro M, Vasques M, Real E, Carmo J, Kunkel M. Automatic hand feature extraction for forensic purposes. Journal of Forensic Science and Research. 2023;7(1):77-82.

20. Bjelan S, Jovanović M, Tatalović V, Kecman S. Synovial sarcoma of the hand – case report and literature review. Med Pregl. 2023;76(7-8):227-31.

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REVIEW ARTICLES
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ARTIFICIAL INTELLIGENCE IN URODYNAMIC STUDIES

UPOTREBA VEŠTAČKE INTELIGENCIJE U URODINAMIČKIM ISPITIVANJIMA

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Review article
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Abstract
Introduction. Urodynamic studies are a fundamental diagnostic tool in functional urology, crucial for assessing urinary tract function. Over the past decade, artificial intelligence has been progressively applied across several scientific disciplines, with healthcare representing a significant area of growth. This review aimed to examine the published literature on the use of machine learning in urodynamics over the preceding five years. **Material and Methods.** A comprehensive literature review was conducted using *Google Scholar* and *PubMed* to identify studies published between 2020 and 2025 on AI applications aimed at reducing the invasiveness of urodynamic testing, enhancing diagnostics, and predicting treatment outcomes. **Results.** Recent studies demonstrate that artificial intelligence and machine learning significantly enhance diagnostic precision and predictive capability in urodynamics. Algorithms including convolutional neural networks, support vector machines, logistic regression, and decision trees accurately classify detrusor overactivity, bladder outlet obstruction, and other urodynamic abnormalities. **Discussion.** Deep learning models excel in analysing complex high-dimensional data, achieving reporting accuracies of up to 100%, whilst conventional machine learning methods provide greater interpretability. AI systems using uroflowmetry data reached diagnostic accuracies of up to 84%, surpassing expert performance. **Conclusion.** Overall, artificial intelligence and machine learning improve the reliability and efficiency of urodynamic assessments, although larger clinical studies are required for validation.
Key words: Urodynamics; Artificial Intelligence; Decision Support Systems, Clinical; Machine Learning

Sažetak
Uvod. Urodinamičke studije predstavljaju važan dijagnostički alat u funkcionalnoj urologiji i od ključnog su značaja za procenu funkcije urinarnog trakta. Tokom poslednje decenije, primetna je sve učestalija upotreba veštačke inteligencije u različitim naučnim disciplinama, uključujući i zdravstvenu zaštitu. Cilj ovog rada bio je da se sprovede pregled literature o primeni mašinskog učenja u urodinamičkim ispitivanjima u poslednjih pet godina. **Materijal i metode.** Sproveden je pregled literature o primeni veštačke inteligencije u urodinamičkim ispitivanjima dostupni u bazi *Google Scholar* i *PubMed* u periodu od 2020. do 2025. godine. **Rezultati.** Sprovedene studije pokazuju da veštačka inteligencija i mašinsko učenje značajno unapređuju dijagnostičku preciznost i sposobnost predviđanja u urodinamičkim ispitivanjima. Algoritmi poput konvolucionih neuronskih mreža, mašina potpornih vektora, logističke regresije i stabala odlučivanja mogu tačno da klasifikuju hiperaktivnost detrusora, subvezikalnu opstrukciju i druge poremećaje. **Diskusija.** Modeli dubokog mašinskog učenja ističu se u analizi složenih, visokodimenzionalnih podataka, postižući tačnost i do 100%, dok konvencionalne metode mašinskog učenja nude veću interpretabilnost. AI sistemi zasnovani na urofloumetrijskim podacima dostigli su dijagnostičku tačnost do 84%, nadmašujući učinak stručnjaka. **Zaključak.** Veštačka inteligencija i mašinsko učenje poboljšavaju pouzdanost i efikasnost urodinamičkih procena, iako su potrebne veće kliničke studije radi validacije.
Ključne reči: urodinamika; veštačka inteligencija; klinički sistemi za podršku odlučivanju; mašinsko učenje

Introduction

Urodynamic studies (UDS) are a fundamental diagnostic tool in functional urology, essential for assessing urinary tract function and facilitating the diagnosis of complex urological disorders. The International Continence Society standard urodynamic evaluation encompasses procedures including free uroflowmetry, postvoid residual assessment, cystometry, and pressure-flow studies. Interpretation of UDS presents distinct challenges owing to the complexity of the data, requiring considerable skill and experience to achieve reliable results. The inherent subjectivity of UDS interpretation, together with heteroge-

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Abbreviations

UDS – urodynamic studies
AI – artificial intelligence
ML – machine learning
BPNN – backpropagation neural network
CNN – convolutional neural network
LR – logistic regression
DL – deep learning
SVM – support vector machine
LUTS – Lower Urinary Tract Symptoms
BCI – bladder contractility index
BOOI – bladder outlet obstruction index
LLM – Large Language Models

neity in clinical practice, highlights the need for tools that improve standardisation and precision [1].

Over the past decade, artificial intelligence (AI) has been progressively applied across several scientific disciplines, with healthcare being a significant area of growth. Emerging technologies focus on machine learning (ML) algorithms, which are becoming increasingly important in the prediction, prevention, diagnosis, and treatment decision-making for a range of diseases. The escalating integration of electronic, digital, and automated technologies within healthcare also broadens the scope of potential ML applications. A substantial body of research exists on the application of machine learning across medical disciplines, including urology, cardiovascular medicine, and geriatrics, reflecting widespread and growing interest within the medical community [2]. Despite considerable emphasis on modern and non-invasive approaches to reduce patient discomfort during UDS, interpretation remains hampered by a substantial degree of inter-observer variability, which significantly undermines diagnostic consistency. ML and AI are being evaluated as means of improving the diagnostic precision of UDS and addressing these inconsistencies. Such developments may also enhance the performance of emerging non-invasive technologies, which typically yield less reliable data [3].

The potential of ML for urodynamic data analysis has been widely discussed. Current evidence suggests that ML is well-suited for analysing urodynamic data; however, current results to date have not yet demonstrated clinical utility [4].

Material and Methods

To perform this narrative review, we conducted a comprehensive literature search using *PubMed* and *Google Scholar* to identify relevant studies published between January 2020 and October 2025 **(Table 1)**. The search combined keywords relating to AI and urodynamics. AI-related search terms comprised: artificial intelligence, machine learning, deep learning, large language model, and ChatGPT. Urodynamics-related terms included: uroflowmetry, urodynamics, urology, lower urinary tract symptoms, overactive bladder, detrusor overactivity, detrusor underactivity, and bladder outlet obstruction.

Inclusion criteria were as follows: studies that utilised AI models to assess, predict, or diagnose lower urinary tract symptoms; studies reporting quantitative evaluations of model performance; and review articles, meta-analyses, or editorials. Exclusion criteria comprised: articles written in languages other than English, publications without available full texts, and articles not related to UDS. Following application of predefined criteria and removal of duplications, a total of 17 studies were included in the final analysis.

Results

Studies published over the past five years highlight the capacity of machine learning and artificial intelligence to improve the diagnostic precision and predictive capability of urodynamics.

Artificial intelligence algorithms may be broadly categorised into two types: conventional ML (excluding deep learning) and deep learning (DL). Conventional ML algorithms are highly interpretable, which makes them particularly useful for diagnostic and prognostic tasks in urinary dysfunctions where evi-

Table 1. The search strategy summary

Items	Specification
Date of search	January 2020 to October 2025
Databases and other sources searched	*PubMed* and *Google Scholar*
Search terms used	Combination of terms: Artificial intelligence OR machine learning OR deep learning OR large language model OR ChatGPT AND uroflowmetry OR urodynamics OR urology OR lower urinary tract symptoms OR overactive bladder OR detrusor overactivity OR detrusor underactivity OR bladder outlet obstruction
Exclusion criteria	Articles written in non-English languages; publications without available full texts; articles that were not related to UDS
Number of studies included	17

Table 2. Differences between Conventional ML and Deep learning models

	Interpretability	Sample size	Clinical utility
Conventional ML	highly interpretable	small datasets	useful for simple diagnostic and prognostic tasks
Deep learning model	limited interpretability	extensive datasets	analysing high-dimensional data

dence-based conclusions are essential. Deep learning is a subset of ML that employs neural networks. In contrast to conventional ML, DL algorithms are adept at extracting complex image features and processing large datasets, making them well-suited to identifying complex curve patterns within UDS. The principal differences between conventional ML and deep learning are summarised in **Table 2.**

However, DL models require large datasets for effective training. Conventional ML models, by contrast, have a simpler internal architecture with greater interpretability, and are frequently supported by visualisation tools that facilitate detailed evaluation. A limitation of conventional ML, however, is its reduced capacity to identify key features within large, high-dimensional, and unstructured clinical data, such as urodynamic tracing curves. Deep learning algorithms, conversely, are capable of analysing high-dimensional data, autonomously extracting features via deep neural networks, and identifying relationships between imaging characteristics and research objectives. Deep learning models are, however, more complex and frequently operate as a "black box", limiting the real-time interpretability and transparency of their decision-making processes [1].

The studies analysed applied both conventional and DL models to urodynamic data, including: back-propagation neural network (BPNN) [5]; convolutional neural network (CNN) [6]; discrete wavelet transformation; exponential moving average [7]; and logistic regression (LR) [8].

Several studies examined different conventional machine learning algorithms for the development of diagnostic models assessing bladder compliance, including support vector machine (SVM), Random Forest, XGBoost, perceptron, and Naive Bayes [9].

Some studies on ML algorithms have demonstrated precision in identifying detrusor overactivity, detrusor underactivity, and other urodynamic abnormalities from tracings. A further body of literature indicates that ML algorithms integrating urodynamic parameters can effectively predict disease severity or outcomes in functional urologic conditions, such as overactive bladder and neurogenic lower urinary tract dysfunction [10].

In the study by Weaver et al., a DL model combined volume-pressure recordings with fluoroscopic images to enable automatic, precise classification of bladder dysfunction severity in a population with spina bifida. Four models were evaluated for predicting the severity of bladder dysfunction: a clinical model using prospectively collected clinical data from videourodynamics studies; a deep learning CNN trained on raw volume-pressure recordings; a deep learning imaging model trained on fluoroscopic images; and an ensemble model averaging the risk probabilities from the volume-pressure and fluoroscopic models [11].

Hobbs et al. developed an ML approach for identifying detrusor overactivity in urodynamic tests. Files were divided into training and test sets, and each file was windowed to generate data subsets. Multiple classification approaches were evaluated, including k-nearest neighbors and SVM with linear, polynomial, and radial basis function kernels, achieving an area under the curve of 91.9%, with a sensitivity of 84.2% and specificity of 86.4% [12].

Zhou et al. developed deep learning models for diagnosing detrusor overactivity. A single-channel CNN and a 3-channel CNN were constructed. The single-channel CNN was trained using detrusor pressure (p Det) alone as the input signal, whilst the 3-channel CNN was trained simultaneously on vesical, abdominal, and detrusor pressure signals. Both CNNs comprised two convolutional CNN layer groups and a traditional BPNN; each layer group contained several convolutional kernels, convolutional layers, and pooling layers. The traditional BPNN served as the classifier, with Softmax activation function in the output layer enabling classification of different signal types, achieving an accuracy of 78.12% for patients without detrusor overactivity and 100% for those with it [3,13].

In the study by Ding et al. ML algorithms were applied to a preliminary analysis of urodynamic studies using 13 urodynamic parameters as inputs. Three ML approaches were evaluated: Decision Tree, LR and SVM. The LR and the SVM models demonstrated the best performance; the top-performing model achieved an average area under the curve of 0.90 (0.90 ± 0.08) [14].

Matsukawa et al. developed a DL model using a neural network for diagnosing lower urinary tract function in men with lower urinary tract symptoms (LUTS), utilising uroflowmetry data alone. A neural network was trained on uroflowmetry waveforms and subsequently used to diagnose LUTS in new patients

based on their waveforms. The architecture comprised alternating convolutional and maximum pooling layers, followed by a global average pooling layer to summarise the waveform's features, and two fully connected layers to convert these features into bladder contractility index (BCI) and bladder outlet obstruction index (BOOI) values. The AI system's estimated BCI and BOOI values showed significant positive correlations with pressure flow study values (BCI: $r = 0.60$, $P < 0.001$; BOOI: $r = 0.46$, $P < 0.001$). The mean diagnostic accuracy of the AI system, based on uroflowmetry data, was 84%, significantly higher than that of urologists (56%) [15].

Jin et al. constructed a long short-term memory deep-learning algorithm for uroflowmetry data. Gammie et al. (2023) identified some key advantages of AI in UDS, including effective performance in noisy surroundings, pattern recognition in unstructured settings, extraction of clinically relevant variables, and potential improvement in objectivity among clinicians. UDS interpretation is highly susceptible to variability depending on the skills of the interpreter. Jin et al. examined sound-based prediction of urinary flow, bladder outlet obstruction, and LUTS, demonstrating that certain algorithms can enhance the interpretation of variations in urine sounds to an accuracy comparable to that of clinicians [16]. Results from all included studies are summarised in **Table 3.**

Large Language Models (LLMs) are a form of AI that utilise a deep neural network architecture and apply concepts from natural language processing. These models employ unsupervised learning to analyse large volumes of text data, learning language patterns, grammatical rules, and contextual nuances. Deep neural networks, consisting of numerous layers of interconnected nodes, analyse sequential data -

Table 3. Included studies overview

Authors	Year	Algorithm type	Import data	Aim	Accuracy
Zhou et al. [5]	2024	BPNN	11 urinary flow indicators, including P.Qbegin, P. Qmax, Qmax	Diagnose BOO	AUC: 0.949 ± 0.060; ACC: 94.4%; SEN: 100%; SPE: 89.3%
Pong et al. [6]	2022	CNN	RMS values, MFCC features (root mean square;mel-frequency cepstral coefficients	Develop a vibration-based diagnostic tool for voiding dysfunction	ACC: 98%; precision: 98.26%; recall: 98.19%; F1-score: 98.19%
Zareen et al. [7]	2022	DWT + EMA filtering	Pves signal	Estimate detrusor pressure	Correlation: 0.895
Cetinel et al. [8]	2022	Multivariate LR	Symptoms, uroflow curve patterns, detrusor pressure	Distinguish BOO and DU	SEN: 82.5%, SPE: 60% for BOO
Ge Z et al. [9]	2022	(SVM), Random Forest, XGBoost, perceptron, logistic regression, and Naive Bayes	73 features (time-domain, frequency-domain, wavelet features)	bladder compliance	AUC: 0.873; ACC: 84%; SEN: 70.41%; SPE: 84.53%
Weaver et al. [11]	2023	CNNs for imaging + pressure-volume data	Volume-pressure measurements, fluoroscopic imaging	Classify bladder dysfunction severity	ACC: 70%, weighted kappa: 0.54
Hobbs et al. [12]	2022	SVM with RBF kernel	Time-based and frequency-domain features from Pves, Pabd, and Pdet	Detect DO	AUC: 0.919 ± 0.013, SEN: 84.2%, SPE: 86.4%
Zhou et al. [13]	2023	Single-channel CNN, 3-channel CNN	Pves, Pabd, Pdet signals with wavelet-denoising preprocessing	Diagnose DO	ACC: 99.99% (train), validation: 99.72% (3-channel CNN)
Ding et al. [14]	2024	DT, LR, SVM	15 urodynamic parameters and demographics	Automate diagnostic system for LUTD	AUC: DT (0.63–0.98), LR (0.73–0.99), SVM (0.64–1.00)
Matsukawa et al. [15]	2021	NN (1D convolutional)	UFM waveform features	Classify LUTD (DU, BOO, DU + BOO)	ACC: 84%; SEN: 79.7%; SPE: 88.7%
Jin et al. [16]	2021	LSTM	Loudness and roughness from uroflow sound signals	Predict and classify bladder emptying patterns using sound signals	ACC: 95%; mean flowrate error: 6%; SEN: high

such as sentences - by predicting the next word on the basis of preceding words, thereby developing a comprehensive understanding of linguistic structure. Reliance on such models without appropriate oversight risks patients bypassing professional consultation, potentially leading to incorrect diagnosis or inappropriate treatment [17,18]. Based on current literature, no original research articles have evaluated LLMs in the diagnosis of urodynamic findings. A few studies examining the role of LLMs in urodynamics quality control have excluded urodynamics trace interpretation, owing to the inability of the ChatGPT version used to analyse images directly [4]. Large language models show potential for quality control and data interpretation, but their diagnostic application in urodynamics remains unexplored.

Discussion

These studies demonstrate that AI and ML models can enhance diagnostic precision and reliability. As these technologies advance, it is likely that AI and ML will be integrated into urodynamics software to deliver automated, real-time data analysis and interpretation. Such integration could streamline clinical processes, reduce diagnostic discrepancies, and improve the accuracy and applicability of urodynamic investigations in routine clinical practice. Nevertheless, further clinical trials are required to improve accuracy and validate these models prior to widespread adoption [3].

Artificial intelligence in urodynamics is advancing rapidly, yet a number of obstacles remain, and visual analysis of the urodynamic trace by a clinician remains the cornerstone of urodynamic diagnosis. **Figure 1** illustrates the potential incorporation of machine learning algorithms into urodynamic studies. Further research into the generalisability of models is needed, as the majority of studies in this field are retrospective, single-centre analyses conducted without external validation.

Furthermore, large volumes of labelled data are required for model training in both conventional ML and DL approaches. Existing studies lack sufficient sample sizes to exclude the possibility of model overfitting and limited generalisability, which severely restricts their clinical applicability. For example, a study that achieved nearly 100% accuracy in detecting detrusor overactivity (DO) enrolled only 92 patients, of whom 44 comprised the test - an inadequately small dataset for a deep learning method. Existing studies have also focused predominantly on a limited number of urodynamic trace parameters, omitting other urodynamic indicators that would be essential for clinical application.

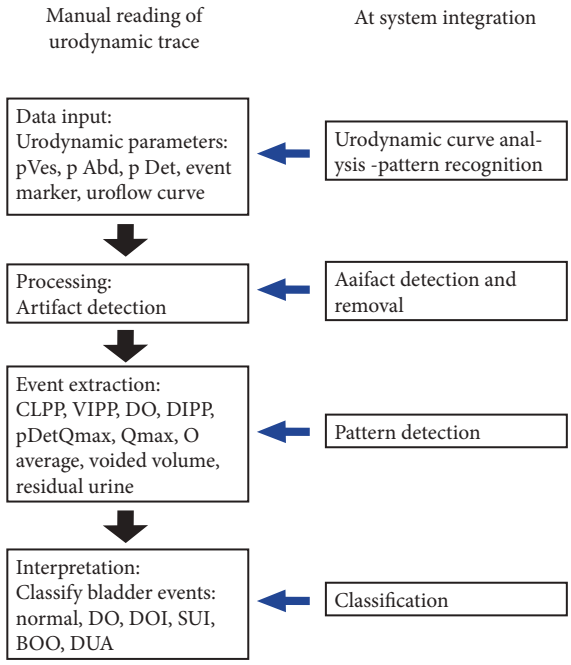

Figure 1. Potential introduction of machine learning algorithms to urodynamic studies

A further limitation is that the majority of studies apply highly specific inclusion and exclusion criteria and recruit patient cohorts that are markedly homogeneous. This highlights the critical importance of external validation studies to determine whether algorithmic models can consistently generalise to different patient populations.

Oversimplification of predictive models represents another drawback. Many models are designed only for binary classification tasks, such as determining whether detrusor overactivity is present or absent. In clinical practice, however, LUTS is frequently multifaceted: a patient may present with detrusor overactivity, detrusor underactivity and bladder outlet obstruction concurrently. Reducing a complex clinical picture to a binary outcome does not adequately reflect the reality of LUTS management.

A major obstacle to AI development in urodynamics is the absence of a consistent, high-quality, multicentre database. Existing urodynamic databases are predominantly single-centre, likely reflecting the lack of agreed diagnostic criteria for UDS and the inter-rater reliability of interpretations. This absence of uniformity further hampers urodynamic AI research. There is an immediate need to establish standardised diagnostic criteria and nomenclature for UDS to advance AI development in this field. Both clinical practice and the integration of AI into UDS would benefit from the adoption of consensus-driven standards. Developing a reliable multicentre urodynamic database is another important step; such a resource, en-

compassing diverse and representative datasets, would facilitate model training and validation. The ability to perform well across a heterogeneous patient population is one of the most important prerequisites for clinical adoption of AI models.

Finally, the risks associated with the misuse of AI in urodynamics must be carefully considered. Whilst AI holds considerable promise, inadequately validated models may lead to diagnostic errors, inappropriate treatment recommendations, or excessive reliance on automated systems. Rigorous validation and verification procedures are necessary to ensure the reliability and safety of AI tools before deployment in clinical settings. Accessing accurate medical information is essential; even a low rate of misinformation can have serious consequences for patients. Given these limitations, close collaboration between AI developers and healthcare professionals is crucial to ensure the safe and effective use of AI in clinical practice.

Conclusion

Machine learning has demonstrated promising predictive and diagnostic capabilities in urodynamic studies, indicating considerable potential for near-future clinical application. However, challenges including a lack of multicentre studies, limited availability of large datasets, and the complexity of clinical conditions continue to restrict its widespread adoption.

References

1. Huang HH, Cheng PY, Tsai CY. Exploring artificial intelligence in functional urology: a comprehensive review. Urol Sci. 2025;36(1):2-10.

2. Wang Q, Wang X, Jiang X, Lin C. Machine learning in female urinary incontinence: a scoping review. Digit Health. 2024;10:20552076241281450.

3. Chew LE, Hannick JH, Woo LL, Weaver JK, Damaser MS. The future of urodynamics: innovations, challenges, and possibilities. Neurourol Urodyn. 2026;45(2):293-8.

4. Zeng X, Mo H, Shen H, Jin T. Evaluating the utility of ChatGPT in addressing conceptual and non-conceptual questions related to urodynamic quality control and trace analysis. Sci Rep. 2025;15(1):20091.

5. Zhou Q, Li G, Cui K, Mao W, Lin D, Yang Z, et al. Using machine learning to construct the diagnosis model of female bladder outlet obstruction based on urodynamic study data. Investig Clin Urol. 2024;65(6):559-66.

6. Pong YH, Tsai VF, Hsu YH, Lee CH, Wang KC, Tsai YT. Application of a deep learning neural network for voiding dysfunction diagnosis using a vibration sensor. Applied Sciences. 2022;12(14):7216.

7. Zareen F, Ouyang Z, Majerus SJ, Bruns TM, Damaser MS, Karam R. Detrusor pressure estimation from single-channel urodynamics. Annu Int Conf IEEE Eng Med Biol Soc. 2022;2022:3718-22.

8. Çetinel B, Önal B, Selçuk B, Can G, Aferin U, Yıldırım Ö. Urodynamic curve patterns may predict female bladder outlet obstruction and detrusor underactivity. Urology. 2022;165:150-6.

9. Ge Z, Tang L, Peng Y, Zhang M, Tang J, Yang X, et al. Design of a rapid diagnostic model for bladder compliance based on real-time intravesical pressure monitoring system. Comput Biol Med. 2022;141:105173.

10. Knorr JM, Werneburg GT. Machine learning and artificial intelligence to improve interpretation of urodynamics. Curr Bladder Dysfunct Rep. 2024;19(1):44-53.

11. Weaver JK, Martin-Olenski M, Logan J, Broms R, Antony M, Van Batavia J, et al. Deep learning of videourodynamics to classify bladder dysfunction severity in patients with spina bifida. J Urol. 2023;209(5):994-1003.

12. Hobbs KT, Choe N, Aksenov LI, Reyes L, Aquino W, Routh JC, et al. Machine learning for urodynamic detection of detrusor overactivity. Urology. 2022;159:247-54.

13. Zhou Q, Chen Z, Wu B, Lin D, Hu Y, Zhang X, et al. A pilot study: detrusor overactivity diagnosis method based on deep learning. Urology. 2023;179:188-95.

14. Ding Z, Zhang W, Wang H, Ke H, Su D, Wang Q, et al. An automatic diagnostic system for the urodynamic study applying in lower urinary tract dysfunction. Int Urol Nephrol. 2023;56(2):441-9.

15. Matsukawa Y, Kameya Y, Takahashi T, Shimazu A, Ishida S, Yamada M, et al. Development of an artificial intelligence diagnostic system for lower urinary tract dysfunction in men. Int J Urol. 2021;28(11):1143-8.

16. Jin J, Chung Y, Kim W, Heo Y, Jeon J, Hoh J, et al. Classification of bladder emptying patterns by LSTM neural network trained using acoustic signatures. Sensors (Basel). 2021;21(16):5328.

17. Eckrich J, Ellinger J, Cox A, Stein J, Ritter M, Blaikie A, et al. Urology consultants versus large language models: potentials and hazards for medical advice in urology. BJUI Compass. 2024;5(5):438-44. Erratum in: BJUI Compass. 2024;5(12):1324-9.

18. Fogt F. The illusion of diagnostic agreement: institutional bias as a hidden force in modern medicine. Med Pregl. 2025;78(5-8):127-31.

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A MULTIDISCIPLINARY APPROACH TO THE MANAGEMENT OF TRAUMATIC FINGER AMPUTATIONS

MULTIDISCIPLINARNI PRISTUP U ZBRINJAVANJU TRAUMATSKIH AMPUTACIJA PRSTIJU

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Abstract
Hand injuries are among the most common musculoskeletal injuries, predominantly affecting working-aged males under 40 years. Traumatic finger amputation refers to the loss of part or all of a finger due to mechanical trauma. The most common injury mechanisms include sharp-cut injuries, contusions, and avulsions. Prompt and thorough assessment is crucial to achieve optimal functional recovery. This narrative review aims to present contemporary treatment concepts, their outcomes, and the specifics of multidisciplinary cooperation among the patient, their family members, and healthcare professionals. A literature search was conducted in January 2026 across *ScienceDirect, Scopus, PubMed*, and *Google Scholar* to identify peer-reviewed articles on traumatic finger amputations and their management. Treatment selection for traumatic finger amputation must be individually tailored to each patient, taking into account the complexity of the wound healing process, the functional specifics of the hand, and the patient's aesthetic and functional expectations. Close collaboration among healthcare professionals, patients, and family members enhances patient-centred care and improves treatment outcomes.
Key words: Finger Injuries; Amputation, Traumatic; Replantation; Wound Healing; Plastic Surgery Procedures; Patient Care Team; Rehabilitation; Treatment Outcome

Sažetak
Povrede šake predstavljaju jedne od najčešćih muskuloskeletnih povreda i obično se javljaju kod radno aktivnih muškaraca mlađih od 40 godina. Traumatska amputacija prsta predstavlja delimičan ili potpun gubitak prsta usled mehaničke traume. Najčešći mehanizmi povređivanja uključuju povrede nastale oštrim predmetima, kontuzije i avulzije. Pravovremena i detaljna procena predstavlja osnov za postizanje optimalnog funkcionalnog oporavka. Cilj ovog preglednog rada bio je da prikaže savremene terapijske pristupe, njihove ishode, kao i značaj multidisciplinarne saradnje između pacijenta, članova porodice i zdravstvenih profesionalaca. Pretraga literature sprovedena je u januaru 2026. godine u okviru baza *ScienceDirect*, *Scopus*, *PubMed* i *Google Scholar* sa ciljem identifikacije recenziranih publikacija koje se odnose na traumatske amputacije prstiju i njihovo zbrinjavanje. Izbor terapijskog pristupa kod traumatskih amputacija prstiju mora biti individualizovan, uzimajući u obzir složenost procesa zarastanja rane, funkcionalne karakteristike šake, kao i estetska i funkcionalna očekivanja pacijenta. Bliska saradnja između lekara, medicinskih sestara, fizioterapeuta i članova porodice pacijenta može značajno unaprediti pristup usmeren na pacijenta i doprineti postizanju povoljnijih ishoda lečenja.
Ključne reči: povrede prstiju; traumatska amputacija; replantacija; zarastanje rana; procedure plasti;ne hirurgije; multidisciplinarni tim; rahabilitacija; ishod lečenja

Introduction

Hand injuries represent a substantial epidemiological burden, accounting for 6.6% to 28.6% of all musculoskeletal trauma, and predominantly affect working-aged males under 40 years [1].

The hand is one of the most functionally important parts of the human body, making it particularly susceptible to injury [2].

Traumatic finger amputation refers to the loss of part or all of a finger as a result of mechanical trauma [3]. The most common mechanisms of injury include sharp-cut, crush, and avulsion injuries, which can be distinguished by the severity of damage to soft tissue structures [4]. Finger injuries commonly occur in occupational settings, predominantly during contact with metal objects and bladed hand tools [5].

Since the thumb, index finger, and middle finger are crucial for grip strength and precision, injuries to these fingers are considered severe. The unique anatomical and functional significance of each affected finger, along with the level of amputation, determines the surgical approach and potential outcomes [6].

Early, structured assessment shapes every subsequent decision about preserving a finger. In high-income countries (HICs), rapid diagnostics, appropriate treatment (conservative or surgical), and long-term rehabilitation are available. In low- and middle-

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Abbreviations

ATLS – advanced trauma life support
BSSH – British Society for Surgery of the Hand
DIP – distal interphalangeal joint
ED – emergency department
HICs – high-income countries
IV – intravenous
LMICs – low- and middle-income countries
MCP – metacarpophalangeal joint
MIU – minor injury unit
NCLF-US – noncontact low-frequency ultrasound
NPWT – negative-pressure wound therapy
PIP – proximal interphalangeal joint
PTSD – post-traumatic stress disorder
LWCA – local wound care alone

income countries (LMICs), access to such standards of care is often limited [7]. Treatment options include replantation, revision amputation, and reconstructive procedures. The goals of replantation are to achieve optimal functional and aesthetic results; however, replantation is not feasible for all patients. Suitability for surgery depends on the patient characteristics, the mechanism of injury, the level of injury, and the duration of ischaemia [4].

Replantation and reconstructive techniques are generally preferred when definitive amputation would result in functional deficits. Unsuccessful primary replantation may necessitate surgical revision, potentially resulting in secondary amputation of the affected finger [6].

Treatment selection depends on the level of amputation and other injury-related factors, which determine the choice between revision amputation and attempted replantation. Patients tend to prefer replantation of the amputated finger, which is thought to lead to better functional outcomes, improved quality of life, and reduced pain [8].

In addition to surgical treatment, conservative options include the application of semi-occlusive wound dressings. These dressings provide a favourable local microenvironment for wound healing and preservation of function, and are characterised by ease of application and cost-effectiveness [9]. Amputation is an extremely traumatic experience for the patient, owing to the injury itself, the surgical treatment, and its consequences. Violation of bodily integrity and pain trigger or exacerbate several psychological difficulties that impair the patient's well-being. Physical disability can lead to despair, depression, anxiety, low self-esteem, and social isolation [10].

Given the epidemiological pattern of injury, the complexity of treatment selection, and the psychological impact on the individual, this narrative review aims to present contemporary treatment concepts, their outcomes, and the specifics of multidisciplinary cooperation among patients, their relatives, and healthcare professionals.

Material and Methods

This study is a narrative review. A literature search was conducted in January 2026 across *ScienceDirect, Scopus, PubMed*, and *Google Scholar* to identify peer-reviewed publications on traumatic finger amputations and their management.

The search was conducted using keywords including "finger amputation", "digit amputation", "fingertip amputation", "hand trauma", "replantation", "reconstructive surgery", "wound healing", and "functional outcome", combined with additional descriptors like "rehabilitation", "psychosocial impact", "epidemiology", and "surgical management".

In this review, the term "finger amputation" was used as an umbrella term.

The review focused on English-language articles published between 2016 and 2026, including clinical and observational studies, books, and systematic and narrative reviews that analysed traumatic finger amputation, replantation procedures, or rehabilitation, and that reported functional, clinical, or psychosocial outcomes. Conference abstracts, letters to the editor, non-peer-reviewed publications, and studies not directly related to traumatic finger amputation or hand trauma were excluded. Professional guidelines were included in the description of clinical management principles. Classic articles were included as they describe classification systems for traumatic finger amputations that remain clinically relevant.

Ethical considerations

As this study analysed previously published articles, ethical approval was not required.

Epidemiological aspects

Understanding the patterns and aetiology of traumatic finger amputations is fundamental to developing targeted prevention strategies, improving rehabilitation services, and optimising outcomes [11]. A bimodal age distribution of incidence has been observed, with the highest rates in children aged 0 to 4 years (door crush injuries) and in adults aged 65 to 74 years, most often during chainsaw operation [12].

In a recent retrospective study conducted at a German trauma centre, the highest incidence of injuries was recorded in male patients; work-related injuries were predominant. A seasonal pattern was observed, with the highest frequency in July and September; the index finger was most commonly injured. Multiple amputations were recorded in 17.5% of cases, predominantly during leisure activities [6].

Risk factors

Many traumatic situations, including workplace accidents, road traffic accidents, and sports injuries,

can lead to finger amputation. Risk factors include insufficient occupational safety training, exposure to hazardous machinery, and improper handling of tools and equipment. Participation in recreational activities involving high speed or working at height also increases the risk of traumatic injury [13].

Classification of traumatic finger amputations

Finger amputation classification is primarily based on amputation level [14].

Several classification systems have been described, including those by Tamai, Allen, Ishikawa et al., and Hirase [5]. Traumatic amputations can also be classified as complete (total) or incomplete (subtotal). In a complete finger amputation, there is no connecting tissue between the amputated segment and the stump. In an incomplete amputation, a soft tissue bridge remains, involving less than one-quarter of the finger circumference [15].

Treatment of Traumatic Finger Amputation

Treatment selection for traumatic finger amputation depends on patient-related and injury-related factors. **Table 1** summarises the algorithm for the initial management of traumatic finger amputations, as outlined in the British Society for Surgery of the Hand (BSSH) guidelines [16].

Available treatment options include both conservative and surgical modalities. Conservative options include semi-occlusive dressings and innovative approaches such as negative-pressure wound therapy (NPWT), whilst surgical options include flap and stump surgery.

Conservative treatment

Patients managed non-operatively typically demonstrate rapid recovery with minimal long-term functional deficits. In healing by secondary intention, the wound is left open to heal through granulation. This approach is recommended for amputations smaller than 2 cm, owing to its simplicity and effectiveness [5].

Occlusive and semi-occlusive film dressings are safe and effective in carefully selected patients. Compared with surgical treatment, they are associated with significant pain reduction, better sensory outcomes, less pronounced cold intolerance, improved aesthetic results, reduced limitations in activities of daily living, and shorter work absence. These characteristics make them an effective alternative in the contemporary management of traumatic fingertip amputations [9,17,18].

In a recent study, NPWT was used as a treatment option for six traumatic finger amputations in five patients in whom replantation was not possible. Mean

Table 1. Algorithm for the management of traumatic finger amputations (according to BSSH guidelines)*

Phase	Procedures/Activities
The first steps in the Emergency Department (ED) and Minor Injury Unit (MIU)	- Bleeding Control (ATLS) - Ring removal - Tetanus prophylaxis according to national guidelines - IV antibiotic administration, according to local protocols - Analgesia, consider nerve block - Treatment and photographing of the wound - Radiography of the wound and amputated part
Handling the amputated part	- If amputated part is available: wrap it in gauze soaked in saline, place it in a sealed plastic bag; put the bag on ice and water - If amputated part is not available: irrigate the wound, prepare for terminalisation
Specialist assessment	- Emergency referral/transfer to a specialist hand surgery unit if indicated - Decide between: replantation, composite grafting, revision amputation - Considering the location of the injury and the feasibility of stable fixation - Shared decision-making with the patient
Timeframes	- Composite graft: up to 12 hours after injury - Replantation: With muscle → up to 4 hours Fingers → up to 24 hours.
Peri- and postoperative care	- Antibiotics according to the open fracture protocol - Vascular status monitoring - Dressing for 5–7 days, then considered individually - Multidisciplinary follow-up for complex cases - Referral to hand therapist and prosthetic service - Consider pharmacological pain management

*Local protocols may vary. The amputated part should be preserved appropriately in accordance with BSSH recommendations. Reported timeframes reflect guideline recommendations and may vary depending on warm- and cold-ischaemia conditions.

healing time was 22.7 days, with complete recovery of sensibility within three months, preserved range of motion and grip strength, and high patient satisfaction with aesthetic outcomes. Slight deformity and nail shortening were observed, with no other complications. In this small series, NPWT led to reliable healing when replantation was not possible, though larger studies are needed to confirm these findings [19].

Combined treatment incorporating semi-occlusive dressings with surgical intervention provides good regeneration of the fingertip across all levels of amputation and necrosis [20].

In addition to standard occlusive dressings, other conservative methods have been described. Gomez et al. demonstrated that non-contact low-frequency ultrasound (NCLF-US), combined with topical wound care, accelerates healing of fingertips without exposed bone compared with local wound care alone (LWCA), even in initially larger amputations [21].

Surgical treatment

Several surgical techniques are available, and the choice of technique depends on the nature of the initial trauma. Their aim are to restore function, optimise aesthetic outcomes, and minimise sensory loss [22].

Composite grafting

Composite grafting is a non-microsurgical method intended for distal fingertip amputations. Its advantages include preserving finger length without donor-site morbidity and restoring motor and sensory function. Adverse events following composite graft application include poor sensibility, tissue colour mismatches, necrosis, and infection [23].

Studies investigating composite grafts in distal fingertip amputations have reported good functional and aesthetic outcomes. Idone et al. [24] reported the effectiveness of the cooling composite graft (Hirase technique) in eight patients. Near complete graft survival was achieved in six cases; in two cases partial necrosis occurred as a consequence of inadequate therapy adherence (inconsistent cooling of the amputated segment during the recommended period). The authors concluded that the cooling composite graft represents a reliable alternative to microsurgical replantation when venous anastomosis is not possible. Similarly, Şener et al. [25] examined the use of composite grafts in the emergency department and operating theatre in 36 patients (22 paediatric). They found no differences in complications, additional interventions, or functional outcomes between the two settings. Emergency department use was significantly less costly and required shorter hospitalisation. At the same time, patient satisfaction did not differ, confirming that composite grafting is a reliable and cost-effective method for distal fingertip amputations.

Replantation

Finger replantation has become the standard treatment for carefully selected patients, particularly with advances in modern microsurgical techniques. Limitations to its wider application include the need for intensive rehabilitation, prolonged work absence, high costs, extended hospital stays, technical complexity, and an insufficient number of highly specialised centres [26].

Favourable treatment outcomes following thumb replantation are well documented in the literature, and thumb amputation is therefore considered a strong indication for replantation [27,28].

Replantation is associated with better functional scores than revision amputation, particularly for amputations above the proximal interphalangeal (PIP) joint in fingers other than the little finger. For the little finger, replantation does not offer a significant functional advantage [29].

According to Lu et al., the overall successful replantation rate is 86.4%. Incomplete amputations are more common than complete amputations, and the mechanism of injury and degree of amputation are the principal factors affecting replant survival [30].

Sharp-cut injuries have significantly better outcomes than crush-degloving injuries. Comminuted fractures and tuft injuries significantly reduce the finger survival rate. Functional outcomes are more unfavourable with high-energy fractures, subzone 4 fractures, and base fractures, as reflected in the reduced range of motion at the distal interphalangeal (DIP) joint [31].

The interaction between adjacent fingers across amputation patterns must be considered when accurately comparing functional outcomes across therapeutic options [29].

Revision amputation

Revision amputation can lead to satisfactory outcomes, particularly with respect to sensibility. The principal disadvantage of this method is the potential for cold intolerance, a consequence of nerve damage, rather than the procedure itself [5].

In severe traumatic injuries between the PIP and metacarpophalangeal (MCP) joints, ray amputation or amputation of the proximal phalanx is considered. Ray amputation is indicated when there is bone loss of the proximal phalanx or loss of PIP joint function. Phantom pain may be more pronounced following stump preservation, whereas patients who undergo ray amputation experience lower pain intensity, but reduced sensitivity. Both procedures have a similar return-to-work time of approximately two months. The choice between the two approaches is primarily based on individual aesthetic and functional considerations [32].

Complications

Complications of traumatic finger amputations are classified as early and late.

Early complications include arterial and venous insufficiency and infection. These typically arise soon after trauma and can significantly affect outcome if not treated promptly. Prevention requires avoiding vasoconstriction, maintaining adequate hydration and normothermia, ensuring adequate analgesia, and careful monitoring for changes in skin colour, turgor, or capillary refill time.

Late complications include cold intolerance (which usually resolves within two years), tendon adhesions, bone malunion (particularly in children), and altered sensory perception. Tenolysis is indicated in severe cases of tendon adhesion, with careful consideration of the risk of devascularisation [3,15].

Although fingertip necrosis may occur early in the postoperative course, secondary reconstructive procedures combined with intensive, long-term rehabilitation can lead to satisfactory functional recovery. Despite a good range of motion and preserved grasp strength, cold intolerance may persist for more than two years [33].

Pang and colleagues identified surgical and anatomical factors as the most important predictors of replant necrosis. Prolonged surgical duration is an independent risk factor for partial or complete necrosis. The level of amputation had a significant impact on outcome, with worse results reported for more distal amputations, attributed to the limited availability of adequate vascular and soft tissue structures for reconstruction [34].

Pain following finger amputation manifests as residual pain and, less commonly, phantom pain, which can be difficult to distinguish from residual pain. Conventional conservative treatments have shown limited efficacy, while secondary surgical interventions do not guarantee lasting relief. Attention is therefore increasingly directed towards surgical techniques that prevent the development of neuropathic pain at the time of amputation – an approach that, in addition to reducing pain, avoids the need for subsequent surgery and analgesia. Such techniques include neurovascular insular lobes, centro-central nerve union, and epineural techniques [35]. A retrospective study by Harris et al. [36] found that bite and sharp-cut injuries were associated with an increased risk of secondary revision. At the same time, the index, middle, and little fingers had a higher risk compared with the thumb. Work-related injuries were also identified as a significant risk factor, and no difference in the frequency of secondary revisions was observed between patients treated in the emergency department and those treated in the operating theatre.

Rehabilitation and orthopaedic devices are essential complements to surgical treatment, optimising return to function and enabling occupational activities. As they form an integral part of management, close collaboration between medical and paramedical teams is of great importance [22].

Nursing interventions

Nursing interventions directly influence treatment outcomes in patients with traumatic finger amputation. Nursing staff play a key role in the initial assessment, which includes taking a history covering the mechanism and timing of injury, the type of force involved, and the patient's medical background. Initial examination of the injured digit allows assessment of potential underlying structural damage [37].

Primary clinical evaluation must promptly identify vascular perfusion disorders, as inadequate blood flow leads to endothelial damage, platelet aggregation, and intravascular fluid loss, thereby impeding neovascularisation and further compromising tissue integrity [38].

Appropriate wound care is essential in preventing infection. Nurses are responsible for ongoing wound management, including correct dressing application and continuous monitoring. This is particularly important for the early recognition of signs of infection in injuries sustained in contaminated environments [37].

An understanding of the psychosocial needs of patients with traumatic finger amputation enables the identification of priorities, appreciation of the patient's subjective experience of the injury, and timely implementation of supportive interventions, thereby improving the quality of care.

Patients initially have a pronounced need for clear information about the functional and aesthetic outcomes and potential treatment complications. Effective communication reduces anxiety, facilitates the expression of emotions, and improves cooperation and trust in healthcare professionals. Family members make a significant contribution to supporting the patient following traumatic amputation; their active involvement in care helps reduce the psychological burden and facilitates the recovery of independence [39].

The application of Orem's self-care deficit theory is particularly relevant in patients with traumatic finger amputation, as impairment of hand function directly affects the ability to perform self-care tasks and activities of daily living. Nurses have an important role in educating patients about self-care behaviours. Patient education should be tailored to cultural context and individual abilities, using plain language and visual aids where applicable. Based on the patient's level of self-care ability or deficit, nurses should conduct individual assessments and adjust these in response to changes in the patient's condition or treatment plan [40].

Rehabilitation and functional recovery

Rehabilitation of patients with complex hand trauma requires a multidimensional approach integrating physical, emotional, and psychological aspects [41].

Rehabilitation should commence as early as possible after surgery, with close collaboration between the patient, surgeon, and physiotherapist. Exercises performed in the early postoperative period, before adequate bone healing has occurred, may lead to undesirable consequences such as pseudoarthrosis. Patients who receive limited physiotherapy in the early postoperative phase, with further rehabilitation initiated once bone healing begins, rarely require secondary reconstructive procedures [42].

Occupational therapy plays a key role in restoring the functions required for daily activities, including dressing, personal hygiene, and eating. An individualised treatment plan includes exercises to improve fine motor skills, assistive devices to compensate for weakness or loss of upper limb function, and education on energy-saving techniques for managing daily activities [41].

Patients who actively participate in the rehabilitation process have a lower incidence of depressive symptoms, clearly indicating the importance of motivation during postoperative recovery [42].

In a comparative study, Bott et al. [43] demonstrated that the long-term range of motion of replanted thumbs shows a degree of recovery comparable to that of the unaffected hand - sensory function after replantation was satisfactory, similar to that following amputation. Patients after replantation reported lower pain both at rest and under load, with no significant differences in overall functional abilities.

Prostheses

Prostheses replace a lost or missing body part in terms of appearance, functionality, or both [44]. Individually designed, customised silicone elastomer prostheses have proved to be the most acceptable option, owing to the faithful reconstruction of the anatomical shape, surface texture and uniformity of skin colour. Silicone elastomers (polysiloxanes) are considered the material of choice for their durability, comfort, stain resistance, and ability to reproduce fine surface details. Additional benefits include protection and desensitisation of hypersensitive amputation sites through constant, gentle pressure [45].

Psychological aspects and mental health outcomes

Traumatic finger amputation affects not only physical function but also psychological well-being. Psychological and emotional support is important immediately after injury, as it helps the patient engage in the rehabilitation process [46].

Psychotherapy helps patients develop coping skills and manage symptoms of anxiety and depression. A multidisciplinary approach enables adequate attention to psychological factors that may adversely affect the course of physical therapy [41].

Approximately 39% of patients with traumatic finger amputation develop prolonged grief reactions or post-traumatic stress disorder (PTSD). Risk factors include absence of replantation, thumb amputation, multiple or proximal amputations, subjective sense of mutilation, and concern about the aesthetic appearance of the hand [47].

Patients frequently report anxiety regarding functional hand impairment and the prospect of becoming dependent on relatives; conversely, they often demonstrate strong intrinsic motivation to engage in rehabilitation and return to daily activities. Uncertainty about functional recovery and the ability to work further intensifies feelings of anxiety and helplessness [48].

Depressive symptoms are common in the first two years after amputation, and both depression and anxiety frequently intensify again during readjustments to daily life following hospital discharge. The role of the mental health professional primarily involves normalising emotional reactions, enhancing communication within the multidisciplinary team, and providing ongoing psychological support. Through this approach, the patient's psychological adaptation to and coping with finger loss can be effectively improved [49].

Patient education and injury prevention

A significant proportion of hand injuries are preventable. Prevention strategies are applicable across all age groups and both sexes, and their implementation is recommended globally, though effective development requires comprehensive knowledge of the epidemiological characteristics of these injuries.

Because traumatic finger amputations are often associated with machinery-related injuries, prevention strategies should address both environmental and behavioural risk factors [50].

The 3E safety concept is an effective prevention framework for most hand injuries:

– Engineering (application of protective hand equipment in the workplace, at home, and in sport; improvement or development of new protective equipment)

– Education (public awareness campaigns; supporting behavioural change)

– Enforcement (guidelines for the safe use of machinery; state regulation of machinery; legislative measures) [50].

The risk of traumatic injury is significantly reduced by occupational safety training and the use of protective equipment such as safety gloves. The in-

stallation of physical barriers and marking of risk zones also help reduce the incidence of injuries [13].

Conclusion

Hand injuries, and traumatic finger amputations in particular, represent a significant clinical and psychological challenge, as patients frequently face fear and anxiety and have many questions about the course of their recovery. Treatment selection for traumatic finger amputations must be tailored to each patient, taking into account the complexity of the wound-healing process, the hand's functional specifics, and the patient's aesthetic and functional expectations. Despite the availability of various conservative and surgical treatment options, further prospective multicentre studies are needed to define therapeutic algorithms more precisely, whilst accounting for the numerous constraints of contemporary clinical practice. Investment in preventive and educational programs to raise awareness of specific occupational risks and the mandatory use of personal protective equipment can significantly reduce the incidence of these injuries. Effective collaboration among surgeons, nurses, physiotherapists, and psychologists, together with the patient and their family members, can greatly enhance the patient-centred approach and contribute to the most favourable treatment outcomes.

References

1. Arroyo-Berezowsky C, Quinzaños-Fresnedo J. Epidemiology of hand and wrist injuries treated in a reference specialty center over a year. Acta Ortop Mex. 2021;35(5):429-35.

2. Višnjevac L, Marčetić B, Janjatov N, Đozić I, Tatalović V, Nikolić J. Gender differences in exposure to hand trauma. Med Pregl. 2024;77(9-12):285-90.

3. Mecca AAQ, Budi AS, Wardhana TH, Hutagalung MR. Epidemiology, classification, etiology, complications, and treatments of finger traumatic amputation: a literature review. World Journal of Advanced Research and Reviews. 2025;25(1):226-30.

4. Treger D, Weinerman J, Cai N, Syros A, Minaie A, Dodds SD. Return-to-work after attempted digit replantation: a systematic review of 31 studies. Hand (N Y). 2026;21(1):21-8.

5. Kawaiah A, Thakur M, Garg S, Kawasmi SH, Hassan A. Fingertip injuries and amputations: a review of the literature. Cureus. 2020;12(5):e8291.

6. Mayrhofer-Schmid M, Aman M, Stolle A, Glaser J, Panayi AC, Rasner AS, et al. Analysis of epidemiology, etiology and injury patterns in 2,179 digit amputations. Sci Rep. 2025;15(1):32657.

7. Crowe CS, Massenburg BB, Morrison SD, Chang J, Friedrich JB, Abady GG, et al. Global trends of hand and wrist trauma: a systematic analysis of fracture and digit amputation using the Global Burden of Disease 2017 Study. Injury Prevention. 2020;26(Suppl 2):i115-24.

8. Kurucan E, Thirukumaran C, Hammert WC. Trends in the management of traumatic upper extremity amputations. J Hand Surg Am. 2020;45(11):1086.e1-11.

9. Esmaeil A, Al-Naseem AO, Lari A, Prada C. Semi-occlusive dressings for the management of fingertip amputations: a systematic review. J Hand Microsurg. 2025;17(3):100241.

10. Roşca AC, Baciu CC, Burtăverde V, Mateizer A. Psychological consequences in patients with amputation of a limb. An interpretative-phenomenological analysis. Front Psychol. 2021; 12:537493.

11. Alaseem A, Alanezi M, Alhuqbani MN, Aldosari ZA, Alkhunein F, Alyahya K, et al. Etiologies and trends in extremity amputations: a ten-year single-center experience. Healthcare (Basel). 2025;13(18):2256.

12. Renfro KN, Eckhoff MD, Trevizo GAG, Dunn JC. Traumatic finger amputations: epidemiology and mechanism of injury, 2010-2019. Hand (N Y). 2024;19(2):278-85.

13. Hernández JRR. Management and treatment of traumatic amputation of phalanges by the surgeon. International Journal of Medical Science and Clinical Research Studies. 2023;3(4):635-7.

14. Zhang L, Azmat CE, Buckley CJ. Digit amputation. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2026 [cited 2026 Jan 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538153/

15. Kawilarang B. Finger replantation injury: approach to diagnosis and treatment in the emergency department. JEBMH. 2020;7(2):102-7.

16. The British Society for Surgery of the Hand. Traumatic amputations of the digits, hand and wrist [Internet]. [cited 2026 Jan 13]. Available from: https://www.bssh.ac.uk/_userfiles/pages/files/professionals/girft/girft-amputations.pdf

17. Pastor T, Hermann P, Haug L, Gueorguiev B, Pastor T, Vögelin E. Semi-occlusive dressing therapy versus surgical treatment in fingertip amputation injuries: a clinical study. Eur J Trauma Emerg Surg. 2023;49(3):1441-7.

18. Zaoui P, Renom M, Loisel F, Vericel S, Obert L, Pluvy I. Occlusive dressings for fingertip amputations: clinical outcomes, pulp regeneration, and dermatoglyphic recovery. JPRAS Open. 2026;48:593-602.

19. Mizutani Y, Tamai S, Nakamura T, Hagiwara Y, Takita T, Kawamura K. Conservative treatment of traumatic finger amputations using negative-pressure wound therapy. J Plast Surg Hand Surg. 2023;58:115-8.

20. Dimitrova-Chakarova P, Prommersberger KJ, van Schoonhoven J, Mühldorfer-Fodor M. Ergebnisse der Behandlung von Fingerkuppendefektverletzungen mit einem semiokklusiven Verband („Folienverband") in Kombination mit operativer Versorgung im Rahmen einer erweiterten Indikationsstellung. Handchir Mikrochir Plast Chir. 2025;57(1):32-43.

21. Gomez RW, Walsh A, Valdes KG, Matullo KS. Enhancing healing with noncontact low-frequency ultrasound in fingertip amputation treatment: a comparative pilot study. J Hand Surg Glob Online. 2025;8(1):100843.

22. Vienne AA. Traumatic amputations. In: Mesplie G, editor. Hand functional anatomy and therapy. Cham: Springer; 2025. p. 153-79.

23. Elameen AM, Dahy AA, Abu-Elsoud A, Gad AA. Factors predicting composite grafts survivability in patients with fingertip amputations; a systematic review and meta-analysis. J Orthop Surg Res. 2024;19(1):765.

24. Idone F, Sisti A, Tassinari J, Nisi G. Cooling composite graft for distal finger amputation: a reliable alternative to microsurgery implantation. In Vivo. 2016;30(4):501-5.

25. Şener K, Çakır A, Ahmedov A, İpteç M, Hanoğlu ND, Altuğ E, et al. Composite graft repair in distal finger injuries: emergency room or operating room? Ulus Travma Acil Cerrahi Derg. 2023;29(7):764-71.

26. Monir JG, Cooke H, Jagiella-Lodise O, McQuillan T, Wagner E, Zelenski NA. Trends in digit replantation and revision amputation in the United States from 2009 to 2019. J Hand Surg Glob Online. 2024;6(6):855-60.

27. Billig JI, Nasser JS, Cho HE, Chou CH, Chung KC. Association of interfacility transfer and patient and hospital characteristics with thumb replantation after traumatic amputation. JAMA Netw Open. 2021;4(2):e2036297.

28. Vosbikian MM. Finger replantation: indications and outcomes. SurgiColl [Internet]. 2024 [cited 2026 Jan 15];2(3). Available from: https://surgicoll.scholasticahq.com/article/92638-finger-replantation-indications-and-outcomes

29. Zhu H, Wang J, Gao T, Tian M, Xia L, Cai Q, et al. Contribution of revision amputation vs replantation for certain digits to functional outcomes after traumatic digit amputations: a comparative study based on multicenter prospective cohort. Int J Surg. 2021;96:106164.

30. Lu YM, Lin YT, Tsai CH, Pan CH, Chen HH, Lee MC. Prognostic factors for attempted finger replantation and revascularisation after traumatic amputation: a 16-year retrospective cohort study. J Hand Surg Asian Pac Vol. 2023;28(2):149-55.

31. Kageyama T, Shiko Y, Osawa M, Kawasaki Y, Miyazaki T, Sakai H, et al. Associations between fracture characteristics and surgical outcomes in distal digit replantation of Tamai zones 1–2. Microsurgery. 2025;45(8):e70142.

32. Dastagir N, Obed D, Dastagir K, Vogt PM. Personalized treatment decisions for traumatic proximal finger amputations: a retrospective cohort study. J Pers Med. 2023;13(2):215.

33. Frasuńska J, Kostka D, Tarnacka B. Rehabilitation after replantation of a non-work-related finger amputation without vascular anastosmosis – case report. Ann Agric Environ Med. 2024;31(3):446-9.

34. Pang X, Xu P, Huang Y, Liu C, Shen Y, Zhang Z, et al. Analysis of risk factors for post-replantation necrosis in complete multi-finger amputation. JPRAS Open. 2025;46:637-45.

35. de Lange JWD, Hundepool CA, Power DM, Rajaratnam V, Duraku LS, Zuidam JM. Prevention is better than cure: surgical methods for neuropathic pain prevention following amputation – a systematic review. J Plast Reconstr Aesthet Surg. 2022;75 (3):948-59.

36. Harris AP, Goodman AD, Gil JA, Sobel AD, Li NY, Raducha JE, et al. Incidence, timing, and risk factors for secondary revision after primary revision of traumatic digit amputations. J Hand Surg Am. 2018;43(11):1040.e1-11.

37. Kearney A, Canty L. Assessment, management and treatment of acute fingertip injuries. Emerg Nurse. 2016;24(3):29-34.

38. Spiers E. Managing vascular compromise of hand and digit replantation following traumatic amputation. Br J Nurs. 2018;27(20):S50-6.

39. Tsoulou V, Karamolegou E. Psychosocial needs after traumatic amputation. Perioperative Nursing (Gorna). 2019;8(2):93-102.

40. Qian S, Ma Y. Application of Orem's self-care model in postoperative rehabilitation of patients undergoing digit replantation. Medicine (Baltimore). 2025;104(3):e40982.

41. Ghiţan AF, Gheorman V, Pîrvu D, Gheorman V, Udriştoiu I, Ciurea ME. A review of psychological outcomes in patients with complex hand trauma: a multidisciplinary approach. Curr Health Sci J. 2023;49(2):143-50.

42. Ugurlar M, Kabakas F, Purisa H, Sezer I, Celikdelen P, Ozcelik IB. Rehabilitation after successful finger replantations. North Clin Istanb. 2016;3(1):22-6.

43. Bott SM, Rachunek K, Medved F, Bott TS, Daigeler A, Wahler T. Functional outcome after digit replantation versus amputation. J Orthop Traumatol. 2022;23(1):35.

44. Hussain S, Shams S, Khan SJ. Impact of medical prostheses. In: Wang L, Yu L, editors. Computer architecture in industrial, biomechanical and biomedical engineering. IntechOpen; 2019.

45. Kaur S, Kaur M, Verma A, Singh T. Restoration of a traumatically amputated finger by a traditional glove-type prosthesis: a case report. Eur J Med Health Sci (Bruss). 2021;3(3):41-5.

46. National Institute for Health and Care Excellence (NICE). Rehabilitation after traumatic injury [Internet]. 2022 [cited 2026 Jan 13]. Available from: https://www.nice.org.uk/guidance/ng211/chapter/Rationale-and-impact

47. Pomares G, Coudane H, Dap F, Dautel G. Psychological effects of traumatic upper-limb amputations. Orthop Traumatol Surg Res. 2020;106(2):297-300.

48. Yu X, Zheng W, An W, Xiang S, Feng N, Cheng Y, et al. Investigation on the relationship between Eysenck personality type and the survival rate of traumatic amputated finger replantation based on preventive psychology. Prev Med. 2023;174:107624.

49. Jo SH, Kang SH, Seo WS, Koo BH, Kim HG, Yun SH. Psychiatric understanding and treatment of patients with amputations. Yeungnam Univ J Med. 2021;38(3):194-201.

50. Vasdeki D, Barmpitsioti A, De Leo A, Dailiana Z. How to prevent hand injuries – review of epidemiological data is the first step in health care management. Injury. 2024;55(3):111327.

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THE STATE OF DENTAL ARCH SUPPORTING ZONES IN CHILDREN IN VOJVODINA

STANJE POTPORNIH ZONA ZUBNIH LUKOVA KOD DECE U VOJVODINI

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Abstract
Introduction. The supporting zone is an orthodontic term that defines the space from the distoproximal surface of the lateral permanent incisor to the mesial surface of the first permanent molar. The aim of this study was to determine the space available within the supporting zones to accommodate the permanent successor teeth in children from Vojvodina aged nine, ten and eleven years, and to assess whether the conditions for the second phase of tooth replacement were present. **Material and Methods.** Study models from patients of the Department of Orthodontics, Clinic of Dental Medicine of Vojvodina, were used. A total of 42 models from patients aged nine, ten and eleven years, with equal representation of both sexes, were analysed. Using Onyx CephTM software and the Moyers analysis, the required space within the supporting zones. The resulting values were compared according to sex, age and jaw quadrant. **Results**. The supporting zone showed sufficient space in 64.3% of cases in the maxilla, and in 54.8% in the mandible. In the remaining 35.7% of maxillary cases and 45.2% of mandibular cases, a lack of space was observed. No statistically significant difference (at a level of 0.05) was found according to sex, age or side of the jaw, whereas a significant difference was found between the maxilla and the mandible. **Conclusion**. The condition of the supporting zones in children in Vojvodina is satisfactory, as are the level and trend of continuous dental care.
Key words: Dental Arch; Child; Dentition, Mixed; Malocclusion; Orthodontics; Dental Care

Sažetak
Uvod. Potporna zona predstavlja prostor ključan za smeštaj stalnih zuba tokom druge faze smene, a njen integritet zavisi od očuvanosti mlečne denticije i rezervnog prostora (engl. *leeway space*). Cilj rada bio je da se ispita raspoloživi prostor u potpornim zonama kod dece uzrasta 9–11 godina u Vojvodini i proceniti uslove za pravilno nicanje stalnih zuba. **Materijal i metode.** Analizirana su 42 studijska modela dece oba pola (9, 10 i 11 godina) sa Klinike za stomatologiju Vojvodine. Mojersovom analizom, uz pomoć programa *Onyx CephTM*, određeni su potreban i raspoloživ prostor u potpornim zonama. Rezultati su poređani prema polu, uzrastu i kvadrantu vilica, uz primenu t-testa. **Rezultati.** Dovoljan prostor u maksili utvrđen je u 64,3%, a u mandibuli u 54,8% slučajeva. Nedostatak prostora zabeležen je u 35,7% u maksili i 45,2% u mandibuli. Nije utvrđena statistički značajna razlika u odnosu na pol, uzrast i stranu vilice ($p > 0,05$), dok razlika između maksile i mandibule jeste značajna. **Zaključak.** Stanje potpornih zona kod dece u Vojvodini je zadovoljavajuće, ali se češće uočava nedostatak prostora u mandibuli, što ukazuje na značaj rane dijagnostike i preventivnih mera.
Ključne reči: zubni luk; dete; mešovita denticija; malokluzija; ortodoncija; stomatološka zdravstvena zaštita

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Introduction

The supporting zone is an orthodontic term that defines the space from the distoproximal surface of the lateral permanent incisor to the mesioproximal surface of the first permanent molar. During the deciduous and mixed dentition periods, this space consists of the deciduous canine, first and second deciduous molars, and diastemas [1]. The most stable diastemas are located between the lateral incisor and canine in the maxilla and between the canine and first molar in the mandible. These diastemas are referred to as primate or anthropoid spaces [2].

The width of deciduous molars together with canines and diastemas is greater than the width of their permanent successors, and this additional space is referred to as the leeway space. The leeway space amounts to 1.5 mm in the maxilla and 2.5 mm in the

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mandible. Its importance lies in accommodating the permanent canine and the first and second premolars, and in permitting the mesial movement of the lower molars to achieve Angle Class I molar relationship and proper intercuspation (the mesial shift) [1,2]. An exception occurs in subjects with Class III malocclusion, in whom the summed crown width of the mandibular incisors exceeds the average value in the general population [3].

Deciduous teeth form a functional unit that serves multiple roles until they are replaced by permanent teeth. They participate in all orofacial functions (breathing, swallowing, mastication, and speech), enable normal jaw growth and development, preserve space for successors, and contribute to facial aesthetics [4,5].

Premature tooth loss or reduced tooth width due to untreated approximal caries can disturb this balance, leading to reduction of the supporting zone, loss of arch length, and development of malocclusions [2,6,7]. Premature tooth loss is defined as loss of a deciduous tooth without eruption of its successor within six months, or when the root of the permanent successor has not developed at least two-thirds, as seen on radiographs [4,8].

Caries and its complications remain the most common aetiological factor of premature tooth loss. Dental trauma, most frequent between ages seven and ten, is another important factor [2].

The rate and extent of space loss depend on the patient's age, the lost tooth, and the available space in the arch. A longer time interval between tooth loss and expected exfoliation leads to greater space loss [2]. The greatest and fastest space loss occurs after extraction of the second deciduous molar, especially in the mandible, and the maxillary canine due to their late replacement. Individuals with primary crowding experience more rapid space loss, while those with spaced dentition usually do not develop crowding or malocclusion [4].

To determine whether the available space is sufficient for permanent canines and premolars, Moyers analysis is used [5]. By summing the mesiodistal widths of the lower four permanent incisors and using Moyers tables, the predicted sizes of teeth in the supporting zone can be determined and compared with arch length. The results may indicate excess space, normal conditions, or lack of space [7,10,12]. Clinically, identifying space deficiency is most important, as it leads to secondary crowding and functional and hygienic complications [13,14].

The aim of this study was to determine the available space in the supporting zones for the accommodation of permanent successor teeth in children from Vojvodina aged nine, ten, and eleven years, and to evaluate differences differences by sex, age, and jaw quadrant.

Material and Methods

The study was conducted in January 2025 at the Clinic of Dental Medicine of Vojvodina, Faculty of Medicine, University of Novi Sad, with approval from the Ethics Committee. It was designed as a cross-sectional study using study models from the Department of Orthodontics.

A total of 42 patient models were analysed (14 per age group), with equal numbers of males and females (21 each), born between 1 January 2006 and 31 December 2009.

Using Onyx CephTM software, the mesiodistal widths of the lower permanent incisors were measured and summed. The boundaries of the supporting zone were defined as the most prominent distal point of the lateral incisor and the mesial point of the first permanent molar.

Moyers' analysis was used to calculate the required, available, and difference spaces for each patient. Results were compared by sex, age, and jaw quadrant. Statistical analysis was performed using the t-test, with results presented in **Tables 1–5.**

Table 1. Dental development stages

0	Tooth germ with no signs of calcification
A	Calcification of individual parts of the occlusal surface, but without fusion
B	Fusion of parts of the occlusal surface; the contour of the occlusal surface is recognisable
C	Crown calcification is complete; dentine deposition begins
D	Tooth crown fully formed up to the cementoenamel junction
E	Root length shorter than crown height
F	Root length equal to or greater than crown height
G	Root formed; apical foramen still open
H	Apical foramen closed

Table 2. Average chronological, dental and skeletal age with difference significance analysis (t-test) for the whole sample

Mean chronological age (years)	10.27±0.92
Mean dental age (years)	10.72±1.82
Mean skeletal age (years)	11.84±1.18
t-test	0.001

Table 3. Average dental age, standard deviation, maximum and minimum values for samples of 9, 10 and 11 years

Chronological age (categories)	9	10	11
Dental age (years)	9.89	11.16	11.39
Standard deviation (SD)	1.21	1.86	2.16
Maximum value	13.7	14.6	14.6
Minimum value	8.3	8.8	7.7

Table 4. Average skeletal age, standard deviation, maximum and minimum values for samples of 9, 10 and 11 years

Chronological age (categories)	9	10	11
Skeletal age (years)	11.62	12.09	11.82
Standard deviation (SD)	1.37	1.02	1.10
Maximum values	13.84	14.19	14.06
Minimum values	8.54	10.45	9.39

Table 5. Average values of dental and skeletal age for 9-, 10- and 11- year olds and difference significance analysis (t-test)

Chronological age (categories)	9 godina	10 godina	11 godina
Mean dental age (years)	9.89	11.16	11.39
Mean skeletal age (years)	11.62	12.09	11.82
Significance of difference (t-test)	0.001	0.05	0.254

Results

Measurement of supporting zones in 42 patients showed that in the maxilla, 27 children (64.3%) had sufficient space, while 15 (35.7%) did not.

In the mandible, 23 children (54.8%) had sufficient space, while 19 (45.2%) did not.

Further analyses showed no statistically significant differences based on age, sex, or side of the jaw. A statistically significant difference was observed between the maxilla and mandible in certain subgroups. Nine-year-olds had sufficient space in both jaws, while 10- and 11-year-olds showed space deficiency in the mandible.

Discussion

The results show a higher prevalence of sufficient space than of insufficient space, indicating relatively favourable conditions for the second phase of tooth replacement.

The findings partially align with studies that identify caries prevalence as a major etiological factor in space loss. Differences between populations highlight the importance of selecting appropriate analytical methods.

Moyers' analysis proved clinically applicable, though caution is advised, particularly in female patients.

No significant differences were found between age groups, sexes, or sides of the jaw, supporting the idea of consistent preventive care and oral health education.

Differences between maxilla and mandible may be explained by variations in caries prevalence and oral hygiene factors.

Conclusion

The condition of supporting zones of dental arches in children in Vojvodina is satisfactory, reflecting an adequate level and trend of continuous dental care.

References

1. Nakaš E, Tiro A, Džemidžić V, Redžebagić-Vražalica L, Ajanović M. Osnovi ortodontske dijagnostike. Sarajevo: Stomatološki fakultet sa klinikama; 2014.

2. Matošević D. Etiologija i terapija preranog gubitka mliječnih zubi. Sonda. 2003;8-9(2):108-13.

3. Puškar N, Puškar M, Vučinić P, Ivić S, Petrović Đ. Determination of dentoalveolar parameters in patients with progenia. Med Pregl. 2022;75(9-10):279-83.

4. Tanić T, Blažej Z, Radojičić J. Posledice prevremenog gubitka mlečnih bočnih zuba. Facta Universitatis Series: Medicine and Biology. 2008;15(2):68-73.

5. Marković M, editor. Ortodoncija. 3rd ed. Beograd-Zagreb: Medicinska knjiga; 1989.

6. Stanić O, Anđelković A, Mirnić J, Predin T. Prevremeni gubitak mlečnih zuba. Medicina danas. 2013;7(1-3):11-5.

7. Visković R,Vujanović M, Brčić V. Prevalencija ortodontskih anomalija te analiza i procjena dentalnog zdravlja djece predškolske dobi unutar triju grupacija u Zadru. Acta Stomatol Croat. 1990;24(4):271-80.

8. Marić D, Vukić-Ćulafić B. Praktikum iz ortodoncije: osnove praktične nastave. 2nd ed. Novi Sad: Medicinski fakultet Novi Sad; 1998.

9. Jović M, Mirnić J, Predin T, Anđelković A. Uloga i značaj držača prostora kao interceptivne stomatološke metode. Medicina danas. 2012;11(10-12):330-3.

10. Lapter V, Slivjanovski D. Ortodontska vrijednost procjene meziodistalnih dimenzija definirane skupine zuba. Acta Stomatol Croat. 1974;8(1):23-7.

11. Lapter V, Slivjanovski D. Dopunska analiza meziodistalnih dimenzija očnjaka i pretkutnjaka. Acta Stomatol Croat. 1975;9(3):113-8.

12. Umićević-Davidović M, Arbutina A, Arapović-Savić M, Marin S. Procena veličine neizniklih stalnih očnjaka i premolara u mešovitoj denticiji. Glasnik Antropološkog društva Srbije. 2012;47:17-25.

13. Khanna R, Pandey RK, Tripathi S. Effect of intermaxillary tooth-size discrepancy on accuracy of prediction equations for mixed dentition space analysis. Eur Arch Paediatr Dent. 2015; 16(2):211-7.

14. Cirulli N, Ballini A, Cantore S, Farronato D, Inchingolo F, Dipalma G, et al. Mixed dentition space analysis of a Southern Italian population: new regression equations for unerupted teeth. J Biol Regul Homeost Agents. 2015;29(2):515-20.

15. Tadić K, Katić V, Špalj S. Učestalost karijesa u pacijenata upućenih na ortodontski pregled. Acta Stomatol Croat. 2018;52 (2):123-31.

16. Miličić A, Gaži-Čoklica V. Razvojne karakteristike kasne mliječne i rane mješovite denticije u prevenciji ortodontskih anomalija. Acta Stomatol Croat. 1980;14(3-4):72-80.

17. Miličić A, Gaži-Čoklica V, Hunski M. Analiza incidencije ortodontskih anomalija i karijesa mliječnih zubi kod zagrebačke djece. Acta Stomatol Croat. 1984;18(2):95-103.

18. Giri J, Pokharel PR, Gyawali R, Timsina J, Pokhrel K. New regression equations for mixed dentition space analysis in Nepalese mongoloids. BMC Oral Health. 2018;18(1):214.

19. Muretić Ž. Važnost prevencijskih mjera u ortodonciji. Acta Stomatol Croat. 1996;30(2):137-40.

20. Ljaljević A, Matijević S, Terzić N, Andjelić J, Mugoša B. Značaj održavanja oralne higijene za zdravlje usta i zuba. Vojnosanit Pregl. 2012;69(1):16-21.

21. Vučemilović Lj. Zdravstveni odgoj u vrtiću. Dijete vrtić obitelj. 2013;(72):30-1.

22. Rajić Z, Valentak Lj, Jukić J. Opravdanost primjene preventivnih mjera u radu sa školskom djecom od 6 do 14 godina. Acta Stomatol Croat. 1995;29(3):159-66.

23. Banu A, Serban C, Pricop M, Urechescu H, Vlaicu B. Dental health between self-perception, clinical evaluation and body image dissatisfaction - a cross-sectional study in mixed dentition pre- pubertal children. BMC Oral Health. 2018;18(1):74.

24. Altherr ER, Koroluk LD, Phillips C. Influence of sex and ethnic tooth-size differences on mixed-dentition space analysis. Am J Orthod Dentofacial Orthop. 2007;132(3):332-9.

25. Mishra RK, Devagiri V. Comparison and testing the reliability of two non-radiographic techniques of mixed dentition space analysis in Nepalese population. Journal of College of Medical Sciences-Nepal. 2017;13(4):410-5.

26. Romić Knežević M, Knežević I, Gabrić Pandurić D. Temporomandibularni poremećaji. Sonda. 2012;13(23):27-31.

27. Šurdilović D, Stojanović I, Apostolović M, Igić M, Kostadinović Lj, Trčković Janjić O. Značaj fosfatnog pufera pljuvačke u evaluaciji učestalosti karijesa kod dece. Acta stomatologica Naissi. 2009;25(59):851-8.

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CASE REPORTS
PRIKAZI SLUČAJEVA

CHALLENGES IN THE ANAESTHETIC CARE OF A CHILD WITH CONFIRMED ALLERGY TO MIDAZOLAM, ATROPINE AND ROCURONIUM – A CASE REPORT

IZAZOVI U ANESTEZIOLOŠKOM ZBRINJAVANJU DETETA SA POTVRĐENOM ALERGIJOM NA MIDAZOLAM, ATROPIN I ROKURONIJUM – PRIKAZ SLUČAJA

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Abstract

Introduction. Drug hypersensitivity reactions represent a major safety concern in anaesthetic practice, particularly in paediatric patients, in whom recognition can be difficult and clinical deterioration may occur rapidly. **Case Report.** We present the case of a 5-year-old child who developed an allergic reaction during a previous general anaesthesia. Based on the results of allergy test results, an individualised anaesthetic plan was developed, including the selection of alternative agents. Anaesthesia was performed successfully with no adverse reactions. **Conclusion.** This case highlights the importance of careful preoperative planning and a personalised approach to ensure the safety of paediatric patients with multiple anaesthetic drug allergies. Even routinely used agents may pose a significant risk, making familiarity with alternative pharmacological options essential for safe perioperative management.

Keywords: Anesthesia, General; Pediatric Anesthesia; Child; Drug Hypersensitivity; Allergy and Immunology; Perioperative Care; Drug-Related Side Effects and Adverse Reactions; Patient Care Planning

Sažetak

Uvod. Reakcije preosetljivosti na lekove predstavljaju jedan od najznačajnijih bezbednosnih problema u anesteziološkoj praksi, posebno u pedijatrijskoj anesteziji, gde je prepoznavanje otežano, a kliničko pogoršanje brzo. **Prikaz slučaja.** U radu je prikazan slučaj deteta, uzrasta pet godina, koje je tokom prethodne opšte anestezije razvilo alergijsku reakciju. Na osnovu dokazanog alergološkog ispitivanja sprovedeno je individualno planiranje anestezije i izbor alternativnih anestetičkih lekova. Anestezija je protekla bez neželjenih reakcija. **Zaključak.** Ovaj slučaj ističe važnost preoperativnog planiranja i personalizovanog pristupa kako bi se osigurala bezbednost pedijatrijskih pacijenata sa višestrukim alergijama na anestetičke lekove. Čak i rutinski korišćeni agensi mogu predstavljati značajan rizik, što čini poznavanje alternativnih farmakoloških opcija neophodnim za bezbedno perioperativno lečenje.

Ključne reči: opšta anestezija; pedijatrijska anestezija; dete; preosetljivost na lekove; alergije i imunologija; perioperativna nega; neželjena dejstva lekova; personalizovani pristup pacijentu

Introduction

Drug hypersensitivity reactions represent a major safety concern in anaesthetic practice. During anaesthesia, multiple drugs are administered over a short period, requiring careful monitoring given the risk of hypersensitivity reactions [1]. Although severe anaphylactic reactions are relatively rare, they can have serious and potentially life-threatening consequences, particularly in the perioperative period [2].

In paediatric anaesthesia, the risk of allergic reactions is further increased by the limited ability to recognise symptoms promptly and by the potential for rapid clinical deterioration. The most common triggers are neuromuscular blocking agents, antibiotics, and latex, while reactions to drugs used for premedication and induction are less frequently reported in the literature [1].

Although hypersensitivity reactions to anaesthetic drugs are extremely rare, when they do occur they can significantly limit the use of standard anaesthetic protocols and necessitate an individualised approach [2].

Midazolam, rocuronium, and atropine are widely used in routine paediatric anaesthetic practice: they

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enable safe premedication and easy separation from parents, and provide airway management, muscle relaxation, and stabilisation of autonomic responses.

In this report, we present the case of a paediatric patient scheduled for surgical ear tube insertion who had experienced an allergic reaction during a previous induction of general anaesthesia. Subsequent allergy testing confirmed allergies to midazolam, atropine, and rocuronium, posing a significant challenge for planning the subsequent anaesthetic management.

Case Report

A 5-year-old boy, weighing 15 kg, was scheduled for surgical ear tube insertion. His medical history was notable for developmental dysphasia and a severe anaphylactic reaction during a previous otorhinolaryngological procedure under general anaesthesia, two years earlier. On that occasion, premedication with midazolam and atropine was followed by sudden agitation, erythema, and dyspnoea. Due to rapid clinical deterioration, general anaesthesia was urgently induced, during which bronchospasm occurred. Subsequent allergological evaluation, including skin prick testing, confirmed hypersensitivity to midazolam, atropine, and rocuronium.

The anaesthesiology team performed a carried out preoperative assessment. A thorough review of the patient's medical records, including his documented and allergologically confirmed drug allergies, informed the development of an individualised anaesthetic plan using alternative drugs to ensure optimal perioperative safety. Informed consent for publication of this study was obtained from the parents.

In line with current recommendations for patients at increased risk of hypersensitivity reactions, corticosteroid premedication was administered. On the day of surgery, prophylactic methylprednisolone was given at a dose of 1 mg/kg. Because of the confirmed midazolam allergy, nebulised dexmedetomidine at 2 μg/kg was administered by inhalation for premedication instead of a benzodiazepine.

Thirty minutes after premedication, the patient was transferred to the operating room. Given the nature of the planned procedure (ear tube insertion), it was decided to proceed with balanced general anaesthesia without endotracheal intubation, using a supraglottic airway device (I-gel) to maintain the airway. In accordance with the anaesthetic plan, anaesthesia was induced with propofol 3 mg/kg and fentanyl 2 μg/kg, consistent with standard paediatric dosing. Given the confirmed rocuronium allergy and the short duration of the procedure, neuromuscular blocking agents were not administered. Anaesthesia was maintained with sevoflurane, with a slightly increased minimum alveolar concentration (MAC) to ensure adequate depth of anaesthesia. Throughout the procedure, vital parameters (heart rate, oxygen saturation, and end-tidal CO_2) remained stable and within age-appropriate physiological ranges. Anaesthesia was discontinued at the end of the procedure. Ondansetron 0.1 mg/kg was administered for prophylaxis against postoperative nausea and vomiting, together with paracetamol 15 mg/kg for postoperative analgesia. The patient awoke from anaesthesia with spontaneous, adequate breathing and stable blood pressure and heart rate. Later that evening, following a repeat clinical assessment, he was discharged home in good general condition, with recommendations for continued follow-up.

Discussion

Perioperative anaphylaxis is a life-threatening condition with an estimated prevalence of 1:3,500 to 1:20,000 procedures and a mortality rate of up to 9%. Clinical presentation includes signs such as skin rash, urticaria, angioedema, bronchospasm, tachycardia, bradycardia, and hypotension [3].

Muscle relaxants are the most common causes (30-70%), followed by antibiotics (8%), chlorhexidine (5%), latex (6%) and others [4,5].

This case illustrates the challenges in the anaesthetic management of a paediatric patient with multiple drug allergies confirmed by allergy testing. Hypersensitivity reactions to midazolam, atropine, and neuromuscular blocking agents are rare. Still, they present a significant clinical challenge, particularly in children, in whom these drugs are frequently part of standard anaesthetic protocols.

Although midazolam is generally regarded as a safe, well-tolerated drug, in some patients it can induce severe adverse reactions, including respiratory depression or arrest and anaphylactoid or anaphylactic reactions [6]. In this patient, the confirmed midazolam allergy required an alternative premedication agent. Dexmedetomidine has emerged as a useful alternative sedative agent in paediatric anaesthesia, as it provides effective sedation with minimal respiratory depression, which may be particularly valuable in patients with a history of perioperative hypersensitivity reactions [7,8].

Neuromuscular blocking agents are among the most common triggers of perioperative anaphylactic reactions, with rocuronium one of the most frequently reported agents [9]. Given the confirmed rocuronium allergy and the short duration of the planned surgical procedure, neuromuscular blockers were avoided, allowing safe anaesthetic management without complications. Where their use is necessary,

cisatracurium may be considered the agent of choice, as it has been reported to carry a lower risk of hypersensitivity reactions and minimal cross-reactivity in patients with confirmed rocuronium allergy [9,10].

Atropine is widely used as an anticholinergic agent in paediatric anaesthesia, owing to the higher incidence of bradycardia in children. Although atropine allergy is extremely rare and not widely recognised among anaesthetists, it is important to be aware of its existence [11,12]. Atropine was therefore omitted from the anaesthetic plan in this case.

Conclusion

This case underscores the critical role of thorough preoperative anaesthetic assessment and detailed history-taking in children with known drug allergies. It also highlights the importance of familiarity with alternative pharmacological options to enable safe anaesthetic management and reduce the risk of perioperative hypersensitivity reactions.

References

1. Baldo BA. Allergic and other adverse reactions to drugs used in anesthesia and surgery. Anesthesiol Perioper Sci. 2023; 1(2):16.

2. Lisiecka MZ. General anesthesia allergy causes and mechanisms. Asia Pac Allergy. 2025;15(3):198-203.

3. Galvão VR, Giavina-Bianchi P, Castells M. Perioperative anaphylaxis. Curr Allergy Asthma Rep. 2014;14(8):452.

4. Krishna MT, York M, Chin T, Gnanakumaran G, Heslegrave J, Derbridge C, et al. Multi-centre retrospective analysis of anaphylaxis during general anaesthesia in the United Kingdom: aetiology and diagnostic performance of acute serum tryptase. Clin Exp Immunol. 2014;178(2):399-404.

5. Mertes PM, Volcheck GW, Garvey LH, Takazawa T, Platt PR, Guttormsen AB, et al. Epidemiology of perioperative anaphylaxis. Presse Med. 2016;45(9):758-67.

6. Nucera E, Aruanno A, Buonomo A, Parrinello G, Rizzi A. Hypersensitivity reaction to midazolam: a case of cardiorespiratory failure. Postepy Dermatol Alergol. 2020;37(6):1012-3.

7. Zhang G, Xin L, Yin Q. Intranasal dexmedetomidine vs. oral midazolam for premedication in children: a systematic review and meta-analysis. Front Pediatr. 2023;11:1264081.

8. Turanjanin Tomić G, Turanjanin D, Rakić G, Fabri-Galamboš I, Bošković N, Uram Benka A. Using low doses of dexmedetomidine for procedural sedation during MRI diagnostics in children – case report. Med Pregl. 2024;77(9-12):348-51.

9. Molero Díez YB, Sanchis Dux R, Sánchez Tabernero Á, de Diego Fernández A. Anaphylaxis to neuromuscular blocking agents: cross-reactivity between rocuronium and cisatracurium. J Can Anesth. 2022;70(2):286-7.

10. Reddy JI, Cooke PJ, van Schalkwyk JM, Hannam JA, Fitzharris P, Mitchell SJ. Anaphylaxis is more common with rocuronium and succinylcholine than with atracurium. Anesthesiology. 2015;122(1):39-45.

11. Samsamshariat S, Honarjoo N, Gheshlaghi F, Dorvashy G, Eizadi-Mood N. Allergic reaction to intravenous atropine in a patient with organophosphate poisoning. J Res Pharm Pract. 2019;8(1):33-4.

12. Thirion C, Pirson F, Momeni M. Parents know best: uncovering a rare allergy during anesthesia consultation. Case Rep Pediatr. 2024;2024:4314186.

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THE FIRST SERBIAN HOSPITAL – 825 YEARS SINCE ITS FOUNDATION AND 850 YEARS SINCE THE BIRTH OF ITS FOUNDER, SAINT SAVA

PRVA SRPSKA BOLNICA – 825 GODINA OD OSNIVANJA I 850 GODINA OD ROĐENJA NJENOG OSNIVAČA, SVETOG SAVE

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Abstract
Rastko Nemanjić – known in monasticism and subsequently canonised as Saint Sava - was born in 1175. In 1198, he restored the abandoned Hilandar monastery on the Athos peninsula in Greece and set out the Hilandar Typikon, composed as an adaptation of the Typikon of the Most Holy Theotokos Evergetida in Constantinople. It devoted Chapter 40 to hospital provisions. The hospital was intended exclusively for the treatment of sick monks, who were cared for by the abbot, attended by one or occasionally two monks, and without a trained physician. To gain the clearest possible insight into the workings of the first Serbian hospital, one should consult the original text of Chapter 40 of the Typikon and translate it as faithfully as possible.
Key words: Hospitals; History of Medicine; Saints; Monks; Famous Persons; History, Medieval

Sažetak
Rastko Nemanjić, u monaštvu Sava, kao svetitelj Sveti Sava, rođen je 1175. godine. Obnovio je zapusteli manastir Hilandar na poluostrvu Atos u Grčkoj 1198. godine. U Hilandarskom tipiku, koji je nastao izvesnim modifikovanjem tipika manastira Presvete Bogorodice Evergetide (Dobrotvorke) iz Konstantinopolja, glava 40 je posvećena bolnici. Ona je bila namenjena isključivo lečenju bolesnih kaluđera. O njima se starao iguman, a opsluživao ih je kaluđer, nekada dva, bez školovanog doktora. Da bi se imao što bolji uvid u rad prve srpske bolnice, treba se pridržavati originalnog teksta Glave 40 tipika koja se odnosi na bolnicu i što tačnije ga treba prevoditi.
Ključne reči: bolnice; istorija medicine; sveci; monasi; poznate ličnosti; istorija, srednji vek

Introduction

Rastko Nemanjić - known in Serbian monasticism as Sava and later canonised as Saint Sava – was well-versed in the law of his time, led the Serbian Orthodox Church to independence, engaged in diplomatic work, played a formative role in Serbian medieval literature, and made a substantial contribution to the development of education. He was, moreover, a prince who became a monk, and the founder of the first Serbian hospital at the Hilandar Monastery on Mount Athos, in Greece, - a peninsula with extra-territorial status and one of the most important centres of Eastern Orthodox monasticism, with Hilandar serving the same role for Serbian Orthodoxy.

Upon completing the construction of the Serbian monastery of Hilandar in 1198, Saint Sava set out the organisation of the monastery and its monastic life in the Hilandar Typikon, including provision for a hospital. The Hilandar Hospital was thus a Serbian hospital outside Serbia, while the first hospital within Serbia itself was at the Studenica Monastery. A small number of scholars consider the Studenica Typikon and the hospital it describes to predate the Hilandar Typikon and its hospital [1].

This represents the oldest written source about Serbian medieval medicine**,** uniting the religious and secular medicine of the period. However, no archaeological evidence survives for it, unlike the monastery hospital at the Monastery of St. George in Dabar (Orahovica Monastery in Mažići near Priboj), described as one of the first, if not the first, archaeologically substantiated medieval hospital buildings at the monastery, based on established Byzantine treatment practice. The monastery was built at the end of the 12th century and renovated in the 14th century. We know with certainty that it was built by the Nemanjić dynasty and renovated by King Milutin [2] - although opposing views also exist [3].

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Saint Sava founded these hospitals in accordance with the decision of the First Council of Nicaea in 325. It was recommended that hospitals, almshouses for the infirm, and lodgings for travellers should be established at Christian monasteries. By founding the hospital, Saint Sava explicitly rejected treatment by witchcraft, sorcery, idolatry and other forms of superstition.

As this year marks 850 years since the birth of Saint Sava and 825 years since the founding of the first Serbian hospital in Hilandar, it is prudent to note that the late 12th and the early 13th century stand out as key periods in the formation of Serbian medicine.

Saint Sava

Rastko Nemanjić – Sava, following his monastic tonsure, was probably born in the village of Mišići near Ras in 1175; however, there are suggestions that his year of birth could have been between 1169 and 1174. Rastko was the youngest of three sons of the Grand Prince Stefan Nemanja and his wife Ana. To prepare him for future state duties, his father granted him, at the age of fifteen, governance of the Hum region (Zahumlje), between the Neretva river and Dubrovnik. However, against his parents' wishes, he renounced worldly life in 1191 (according to other sources in 1192), at the age of 17 or 18, and "went to Mount Athos (the Holy Mountain), already literate and educated in the works of early Christian, Byzantine and Old Slavic literature" [4]. He received monastic tonsure at the Russian monastery of Saint Panteleimon (Old Rusik) and, in 1192, became a monk at the Greek monastery of Vatopedi, where he was given the name Sava, after Saint Sava of Jerusalem (who died in 531 or 532).

Sava remained at Vatopedi for the following seven years, devoting himself to the study of religious and ecclesiastical rules, asceticism and the ascetic life, helping the poor (made possible by the support of his wealthy father), and traveling across Mount Athos, while also learning the writing and translation of church texts.

In the middle of 1198, Saint Sava, together with his father, Simeon, as co-founder, restored the abandoned Hilandar monastery with the permission of the Athos prot (elder) and the Byzantine emperor, for which Sava travelled to Constantinople in 1198 and 1199. Stefan Nemanja, Rastko's father, had become a monk in 1196 at the Studenica monastery, taking the name Simeon, after voluntarily abdicating in favour of his middle son Stefan. His wife, Ana, also became a nun at the same time, continuing her life as Anastasia at the Church of the Virgin Mary in Kuršumlija, in Toplica - a foundation of Stefan. She died four months after her husband, at the age of 75.

The Hilandar monastery was elevated to the status of an independent, imperial monastery, with the church dedicated to the Presentation of the Most Holy Theotokos. Sveti Sava was ordained archimandrite in Thessaloniki around 1201 by the Ecumenical Patriarch of Constantinople (**Figure 1**).

Saint Sava remained in Kareya, the administrative centre of Mount Athos, and at Hilandar until 1206-1207, when he departed for Serbia following the conquest of Mount Athos and Constantinople by the Latins in 1204 and the establishment of the Latin Empire (1204-1261), under the jurisdiction of the Vatican. He then transferred to Studenica - the relics of his father, Simeon, who had lived on Mount Athos from 1197 and died at the age of 86 at Hilandar in February 1199, after eight month' residence. Saint Sava remained at Studenica until 1217, when, with circumstances improved, he returned to Hilandar.

At Nicaea, where the Ecumenical Patriarch and the Byzantine Emperor were residing following the occupation of Constantinople, Saint Sava secured autocephaly – full administrative independence - for the Serbian Church within an independent state of Serbia at the end of 1219. That same year, he was ordained by the Ecumenical Patriarch as the first Ser-

Figure 1. Saint Sava (Fresco in the Mileševa Monastery from the 13th century, made during the life of Saint Sava.)

bian Archbishop, with the archbishopric seated in Žiča, after which he returned to Serbia.

Saint Sava undertook two pilgrimages to the Holy Land, in 1229-1230 and 1234-1235. He did not survive the journey home from the second pilgrimage, during which he had acquired valuable gifts, including camphor, balsam oil, xylaloe, sugar and dates [5]. He died on 14 January 1235 [6], at the age of 60, in Trnovo, Bulgaria, where he was buried; his relics were transferred to the Mileševa monastery in Serbia in 1237, giving rise to the cult of Saint Sava, which endures to this day.

However, disagreement persists regarding the length of his life (60, 62 or 67 years), the year of his death (1235 or 1236), the dating of the transfer of his relics to Mileševa (1237-1241), and their burning at Vračar in Belgrade (variously dated at 1594 to 1597), with some accounts disputing that the burning occured at all [7]. Such uncertainty is understandable given the historical distance involved, since scholars must be "guided by the principle of scientific objectivity, base their conclusions exclusively on verified historical data" [8].

The Hilandar Typikon

To regulate life in the Hilandar Monastery, Saint Sava composed the Hilandar Typikon, following the Kareya Typikon. At the same time, after his father died in 1199, he resided at Kareya, where he built a hermitage dedicated to Saint Sava the Sanctified.

Typikon is a Greek term meaning "blueprint" or "rule". In ecclesiastical usage, it denotes a church constitution setting out the rules and procedures governing the performance of divine services throughout the year, and the life and work of the monks – in essence, the whole life of the monastery - and was read aloud to those who live there. This church-legal document was among the most significant of monastic texts, serving as a model for the functioning and organisation of other Serbian monasteries, both on Mount Athos and in Serbia.

The original Hilandar Typikon has not survived, but an early copy, probably dating from the 1320s, is preserved in the Hilandar library under catalogue number CHIL AS 156.

The Hilandar Typikon was modelled on a comparable text from the Monastery of the Mother of God Evergetis in Constantinople, a site the Nemanjić dynasty often visited and generously endowed. It is not a simple copy of that typikon, but a text adapted to Serbian circumstances and to the customs of Mount Athos, in whose preparation Saint Sava himself took part. "Such a rearrangement created a somewhat different typikon that is at the same time similar to the Evergetid typikon, but also different from it in terms of severity, because some of the overly strict requirements for monks were somewhat mitigated" [9]. This difference is evident, among other places, in Chapter 40 (Chapter 41 in the Euergetid Typikon), which concerns the establishment of a hospital.

Hilandar Hospital

"Monastery hospitals were built (alongside monasteries) following the model of the Orthodox East... and were not a complete copy of the Greek monastery hospitals" [10]. Hilandar Hospital served as the model for other Serbian monastic hospitals that were subsequently established.

Chapter 40 of the Hilandar Typikon concerns the establishment of the hospital. Its ***title,*** in Serbo-Slavic, reads: „О больници и о работајуштих болемь", which translates literally as "On the hospital and those who serve the sick". However, it is generally rendered as "On the hospital and the hospitalist".

Even at the time the Typikon was composed, the word "hospital" was already in use, , spelt as it is today, and requiring no translation (**Figure 2**). The remaining words of the title, „работајуштих болемь", translate as "serving the sick". The corresponding title of Chapter 41 of the Evergetid Typikon – Chapter 40 of the Hilandar Typikon - reads "Περὶ τοῦ

Глава 40 670

О болници и о болничарима

Figure 2. Chapter 40 of the Hilandar Typikon

ναχορτουου καὶ τῶν ἀρρώστων”, translating as “About the hospital and the sick”. Neither the title nor the text refers to hospitalists as such; rather, the sick should be assigned “two servants who will be completely at their service” [11]. A question therefore remains as to whether part of Chapter 40 can be translated as “hospitalist” implying formal training on the part of those who cared for the sick, or whether a strictly literal translation should be preferred.

The word “Ukrop” is the term most often subject to inconsistent interpretation. Some scholars, particularly from the not-so-distant past, leave it untranslated or it is translated as warm water or water to be heated [1,10,12–16], consistent with the meaning in Old Russian, Old Slavonic, Bulgarian, Czech and Polish [17]. Because the term remains undefined and untranslated, it gives authors room to interpret in the context of the term “hospital”. As “hospital” occupies a central place in Chapter 40, some scholars have inferred that “ukrop” carried a medicinal sense, and accordingly translate the phrase “topiti ukrop” as the preparation of medicines, teas, ointments, compresses, food, and drinks [18–20], “although not explicitly stated, the use of medicinal herbs is implied” [16]. Neither Chapter 40 nor any other part of the Typikon makes references to plants, though this does not preclude such information appearing in another document.

The word “ukrop” corresponds to the Greek “τὰ μαγειρεύματα” (to mageireumata) in the original Evergetid Typikon, Chapter 41, meaning “cooked dishes”. In the Serbian translation, the full sentence reads: “that hot dishes and other things be prepared at their request” [11]. This is supported by the translation of part of Chapter 40 of the Studenica Typikon: “And on it you will “ukrop topiti“ for the sick and other things for their comfort, where possible, about food and drink and other needs” [9]. Of sick monks, Chapter 29 of the Hilandar Typikon states that they “having fallen ill, require better food and drink, to strengthen their weakened bodies” [13].

The modern interpretation of “ukrop” is therefore an interpretation rather than a literal translation, as the main text does not provide enough information to fully understand its use. As expected, interpretations can vary between scholars who translated the text.

“The hospitals were not hospitals in the true sense, as they had no physicians...physicians are not mentioned in the Hilandar and Studenica Typikons” [21]. Unlike the Evergetid Typikon, the Hilandar hospital could not draw on trained medical staff, i.e. **physicians**. The Evergetid Typikon states “And, where possible [a physician should be appointed], who should visit the hospital not superficially or occasionally, but daily and wholeheartedly, attending to the brothers and providing each with what is needed” [11]. In Chapter 40 of the Hilandar Typikon, the hospital was instead overseen by the abbot, who likewise attended to the sick, alongside the attendants at his disposal: “And the abbot shall always, not occasionally, come to the hospital and visit the brothers with all his heart and bring what is necessary to everyone” [13]. It is evident that Saint Sava understood the practical constraints on securing a trained physician, relying instead on empirical practitioners who have learned medicine as a craft rather than a formal discipline.

The hospital was located within the monastery and was subject to two principal constraints: its *restricted access* and its limited *space*.

As a closed institution, the hospital admitted only members of the monastic brotherhood - the monks themselves - for treatment; it was not intended for those outside the brotherhood, even if they were sick. Those without monastic affiliation, such as “foreign brothers, the hungry, the exhausted, the naked, and the barefoot” were instead received at the gate or at the guest house (inn), as mentioned in Chapter 11 or 38, of the Hilandar Typikon [12].

The hospital was also constrained spatially, as the Typikon required that only a single room be set aside for these purposes. Drawing on the example of the Evergetid Monastery hospital, this room is thought to have accommodation for about 7-8 beds. So, the hospital was not, as some authors state, “it seems” [18] “a hospital for patients with chronic and incurable diseases (leprosy, paralysis, epilepsy, mental illnesses)” [18,20,22–24].

Chapter 40 of the Hilandar Typikon clearly demonstrates Saint Sava’s commitment to caring for the sick through the organised and responsible provision of hospitals. It is unlikely, however, that this first hospital practised scientific medicine in any substantive sense, that it was a medical center where new diagnostic and therapeutic methods were applied in treatment, as some authors state, that it was a medical school and that “the medical knowledge of Serbian health workers of that time did not differ in any way from their colleagues from the West”, “that Hilandar had the importance of a university in the 13th and 14th centuries” [20,23–25].

Conclusion

Saint Sava, whose 850th anniversary of birth is currently being celebrated, founded the first Serbian hospital in the Hilandar Monastery in 1198-1200 - an exceptionally significant step in the development of medicine among the Serbs. The hospital attended to both spiritual and bodily healing: Saint Sava united

the religious and secular medicine of his time, demonstrating a deep sense of Christian love, care for one's neighbour, and the treatment of the sick, together with a close connection of faith, knowledge, and charity.

The establishment of the first Serbian hospital, although modest, represented a significant step forward for Serbia at the time. Saint Sava exerted a lasting influence on the development of Serbian spirituality, culture, and medicine. There remains a need to interpret as precisely as possible the meaning of individual words and terms from Chapter 40 concerning the hospital – including the word "ukrop" – so that origins of formal medicine might be understood as clearly and reliably as possible.

References

1. Barišić R. Hilandarske bolnice [Hilandar hospital]. In: Živojinović M, Milosavljević M, editors. Četvrta kazivanja o Svetoj Gori [Fourth narrations about Mount Athos]. Beograd: Prosveta; 2005. p. 407-25.

2. Milosavljević D. Fenomen vizantijske bolnice Sv. Georgija u Dabru (Mažićima kod Priboja) [The phenomenon of the Byzantine hospital of St George's monastery in Dabar (Mažići near Priboj). In: Rakocija M, editor. Niš i Vizantija II: zbornik radova II [Niš and Byzantium II]: proceedings II. 2003 Jun 3-5; Niš, Srbija. Niš: Prosveta; 2004. p. 79-95.

3. Popović S. Problemi proučavanja srednjovekovnog nasleđa u Polimlju [Problems in the study of the medieval heritage in the Lim valley]. Starinar. 1994;(55):181-95.

4. Bogdanović D. Sveti Sava [Saint Sava]. In: Sveti Sava: sabrani spisi [Saint Sava collected writings] [Inernet]. 1999 [cited 2025 Nov 4]. Available from: https://www.rastko.rs/knjizevnost/liturgicka/svsava-sabrana/svsava-sabrana_01.html

5. Savić AZ. Darovi sa Nila: novi pogled na susret svetog Save sa egipatskim sultanom [Gifts from the Nile: a new perspective on St Sava's encounter with the sultan of Egypt]. Zbornik Matice srpske za istoriju. 2014;90:7-35.

6. Komatina I. O godini smrti Svetog Save Srpskog [On the year of the death of Saint Sava of Serbia]. Istorijski časopis. 2022; 71:121-47.

7. Dragović M. Sveti Sava nije spaljen: istorijska rasprava [Saint Sava was not burned: historical discussion]. Požarevac: Štamparija, pečatoreznica i knjigoveznica "Jadran"; 1930.

8. Sajlović M. Osnivanje Hilandara: na putu crkvene autokefalnosti Srba [The founding of Hilandar: on the path to the church autocephaly of the Serbian Orthodox Church]. In: Jeftić A, Knežević M, Kisić R, editors. Vera i misao u vrtlogu vremena: Međunarodni zbornik radova u čast mitropolita Amfilohija (Radovića) i episkopa Atanasija (Jevtića) [Faith and thought in the vortex of time: international proceedings of papers in honor of Metropolitan Amfilohije (Radović) and Bishop Atanasije (Jevtić). Beograd: Pravoslavni bogoslovski fakultet Univerziteta; 2021. p. 219-42.

9. Jovanović T. Sveti Sava: sabrana dela [Saint Sava: collected works]. Beograd: Srpska književna zajednica; 1998.

10. Pavlović L. Srpske manastirske bolnice u doba Nemanjića [Serbian monastery hospitals in the Nemanjić era. Zbornik Pravoslavnog bogoslovskog fakulteta. 1951;2:555-66.

11. Anđelković M, Rakićević T, editors. Evergetidski tipik [Evergetis typikon]. Studenica: Manastir Studenica; 2020.

12. Mirković L. Hilandarski tipik Svetog Save [Hilandar typikon of Saint Sava]. Beograd: Državna štamparija Kraljevine Jugoslavije; 1935.

13. Bogdanović D, editor. Hilandarski tipik: rukopis CHIL AS 15. Beograd: Narodna biblioteka Srbije; 1995.

14. Živojinović M. Istorija Hilandara: od osnivanja manastira 1198. do 1335. godine [History of Hilandar 1: from the foundation of the monastery in 1198 to 1335. Beograd: Prosveta; 1998.

15. Savić R. Visoki dometi srpske medicine i zdravstvene kulture u srednjem veku [High score of Serbian medicine and health culture in Middle Ages]. Arhiv za istoriju zdravstvene kulture Srbije. 1983-1984;(12-13):5-22.

16. Bojanin S. Lečenje biljem u srednjovekovnoj Srbiji. Osnovni pregled. Godišnjak za društvenu istoriju. 2012;19(1):7-34.

17. Jelenković A, Ranković Z. O ustrojstvu prvih bolnica kod Srba [On the organization of the first hospitals among the Serbs]. In: Dimitrijević B, editor. 800 godina srpske medicine: zbornik radova [800 years of Serbian medicine: proceedings]. Beograd: Infinitas, Srpsko lekarsko društvo; 2011. p. 25-34.

18. Katić R. Bolnica Svetog Save u manastiru Studenici [Hospital of Saint Sava in the Studenica Monastery]. In: Osam vekova Studenice: zbornik radova [Eight Centuries of Studenica: proceedings]. Belgrade; 1986. p. 201-6.

19. Pavlović B. Manastirske bolnice u srednjovekovnoj Srbiji [The hospitals of the monasteries in the medieval Serbia]. Crkvene studije. 2004;1:381-8.

20. Koprivica M. "Utočište bolesnim i nemoćnima" - bolnice i stacionari pod okriljem srpskih srednjovekovnih manastira [Sanctuary for the sick and the poor - health resorts and hospitals under the auspices of Serbian medieval monasteries. In: Mišić S, Mitrović K, editos. Pošasti na tlu srednjovekovnih srpskih zemljama (epidemije-nepogode-glad) [Plagues on the medieval Serbian countries (epidemics-disasters-famine)]. Beograd: Univerzitet u Beogradu, Filozofski fakultet; 2021; p.117-31.

21. Mirković L. Nešto o vizantijskim i srpskim bolnicama u srednjem veku [Something about Byzantine and Serbian hospitals in the Middle Ages]. Glasnik srpske pravoslavne crkve. 1963;44(10):384-91.

22. Gavrilović V. Bolnice [Hospitals]. In: Ćirković S, Mihaljčić R, editors. Leksikon srpskog srednjeg veka [Lexicon of the Serbian Middle Ages]. Beograd: Znanje; 1999. p. 4-6.

23. Ilić-Tasić S, Pantović M, Jović N, Ravanić D, Obradović D, Sretenović S, et al. Lečenje epilepsije u srpskim srednjovekovnim manastirskim bolnicama [Epilepsy treatment in Serbian medieval monastery hospitals]. Srp Arch Celok Lek. 2009;137(11-12):702-5.

24. Lugonjić MS, Arsenijević OM. Kultura pamćenja začetaka srpske medicine [Culture of memory of the beginning of Serbian medicine]. Baština. 2021;(54):161-78.

25. Katić RV. Srpska srednjovekovna medicina [Serbian medieval medicine]. Gornji Milanovac: Dečje novine; 1990.

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